

WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 1 through 10 of 17 returned.****1. Document ID: US 20020009730 A1**

L1: Entry 1 of 17

File: PGPB

Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020009730
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009730 A1

TITLE: Human stress array

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chenchik, Alex	Palo Alto	CA	US	
Lukashev, Matvey E.	Newton	MA	US	

US-CL-CURRENT: 435/6; 536/24.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KOMC
Drawn Desc	Image										

2. Document ID: US 20010044414 A1

L1: Entry 2 of 17

File: PGPB

Nov 22, 2001

PGPUB-DOCUMENT-NUMBER: 20010044414
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010044414 A1

TITLE: Metastasis genes and uses thereof

PUBLICATION-DATE: November 22, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Clark, Edwin A.	Ashland	MA	US	
Golub, Todd R.	Newton	MA	US	
Hynes, Richard O.	Winchester	MA	US	
Lander, Eric S.	Cambridge	MA	US	

US-CL-CURRENT: 514/44; 435/6, 435/7.23

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KOMC
Drawn Desc	Image										

3. Document ID: US 6352694 B1

L1: Entry 3 of 17

File: USPT

Mar 5, 2002

US-PAT-NO: 6352694

DOCUMENT-IDENTIFIER: US 6352694 B1

TITLE: Methods for inducing a population of T cells to proliferate using agents which recognize TCR/CD3 and ligands which stimulate an accessory molecule on the surface of the T cells

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC
Draw Desc Image											

4. Document ID: US 6350581 B1

L1: Entry 4 of 17

File: USPT

Feb 26, 2002

US-PAT-NO: 6350581

DOCUMENT-IDENTIFIER: US 6350581 B1

TITLE: Tumor-associated antigen

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC
Draw Desc Image											

5. Document ID: US 6342581 B1

L1: Entry 5 of 17

File: USPT

Jan 29, 2002

US-PAT-NO: 6342581

DOCUMENT-IDENTIFIER: US 6342581 B1

TITLE: Secreted protein HLHFP03

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC
Draw Desc Image											

6. Document ID: US 6335170 B1

L1: Entry 6 of 17

File: USPT

Jan 1, 2002

US-PAT-NO: 6335170

DOCUMENT-IDENTIFIER: US 6335170 B1

TITLE: Gene expression in bladder tumors

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC
Draw Desc Image											

7. Document ID: US 6331396 B1

L1: Entry 7 of 17

File: USPT

Dec 18, 2001

US-PAT-NO: 6331396

DOCUMENT-IDENTIFIER: US 6331396 B1

TITLE: Arrays for identifying agents which mimic or inhibit the activity of interferons

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw	Desc	Image								

█ 8. Document ID: US 6245898 B1

L1: Entry 8 of 17

File: USPT

Jun 12, 2001

US-PAT-NO: 6245898

DOCUMENT-IDENTIFIER: US 6245898 B1

TITLE: Monoclonal antibodies that recognize antigens associated with tumor metastasis

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw	Desc	Image								

█ 9. Document ID: US 6033870 A

L1: Entry 9 of 17

File: USPT

Mar 7, 2000

US-PAT-NO: 6033870

DOCUMENT-IDENTIFIER: US 6033870 A

TITLE: Human transmembrane protein

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw	Desc	Image								

█ 10. Document ID: US 5939270 A

L1: Entry 10 of 17

File: USPT

Aug 17, 1999

US-PAT-NO: 5939270

DOCUMENT-IDENTIFIER: US 5939270 A

TITLE: Markers for organ rejection

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw	Desc	Image								

Generate Collection

Print

Term	Documents
CD81.DWPI,EPAB,JPAB,USPT,PGPB.	34
CD81S	0
CD-81.DWPI,EPAB,JPAB,USPT,PGPB.	1
CD-81S	0
TAPA-1.DWPI,EPAB,JPAB,USPT,PGPB.	21
TAPA-1S	0
ANTISENSS	0
ANTISENS.DWPI,EPAB,JPAB,USPT,PGPB.	24
ANTISENSC.DWPI,EPAB,JPAB,USPT,PGPB.	6
ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	19333
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
((CD81 OR CD-81 OR TAPA-1) AND (ANTISENSS\$ OR RIBOZYM\$)).USPT,PGPB,JPAB,EPAB,DWPI.	17

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Display Format:

[Previous Page](#) [Next Page](#)

WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 11 through 17 of 17 returned.****11. Document ID: US 5922566 A**

L1: Entry 11 of 17

File: USPT

Jul 13, 1999

US-PAT-NO: 5922566

DOCUMENT-IDENTIFIER: US 5922566 A

TITLE: Tumor-associated antigen

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KOMC
Draw Desc	Image									

12. Document ID: US 5883223 A

L1: Entry 12 of 17

File: USPT

Mar 16, 1999

US-PAT-NO: 5883223

DOCUMENT-IDENTIFIER: US 5883223 A

TITLE: CD9 antigen peptides and antibodies thereto

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KOMC
Draw Desc	Image									

13. Document ID: US 5863735 A

L1: Entry 13 of 17

File: USPT

Jan 26, 1999

US-PAT-NO: 5863735

DOCUMENT-IDENTIFIER: US 5863735 A

TITLE: Human transmembrane 4 superfamily protein

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KOMC
Draw Desc	Image									

14. Document ID: US 5858358 A

L1: Entry 14 of 17

File: USPT

Jan 12, 1999

US-PAT-NO: 5858358

DOCUMENT-IDENTIFIER: US 5858358 A

TITLE: Methods for selectively stimulating proliferation of T cells

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw Desc	Image									

15. Document ID: US 5854022 A

L1: Entry 15 of 17

File: USPT

Dec 29, 1998

US-PAT-NO: 5854022

DOCUMENT-IDENTIFIER: US 5854022 A

TITLE: Polynucleotides encoding a CD53-like transmembrane protein

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw Desc	Image									

16. Document ID: US 5753516 A

L1: Entry 16 of 17

File: USPT

May 19, 1998

US-PAT-NO: 5753516

DOCUMENT-IDENTIFIER: US 5753516 A

TITLE: Screening method for ligands of the EBI-1 receptor

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw Desc	Image									

17. Document ID: US 5686072 A

L1: Entry 17 of 17

File: USPT

Nov 11, 1997

US-PAT-NO: 5686072

DOCUMENT-IDENTIFIER: US 5686072 A

TITLE: Epitope-specific monoclonal antibodies and immunotoxins and uses thereof

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KIMC
Draw Desc	Image									

[Generate Collection](#)

[Print](#)

Term	Documents
CD81.DWPI,EPAB,JPAB,USPT,PGPB.	34
CD81S	0
CD-81.DWPI,EPAB,JPAB,USPT,PGPB.	1
CD-81S	0
TAPA-1.DWPI,EPAB,JPAB,USPT,PGPB.	21
TAPA-1S	0
ANTISENSS	0
ANTISENS.DWPI,EPAB,JPAB,USPT,PGPB.	24
ANTISENSC.DWPI,EPAB,JPAB,USPT,PGPB.	6
ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	19333
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
((CD81 OR CD-81 OR TAPA-1) AND (ANTISENS\$ OR RIBOZYMS\$)).USPT,PGPB,JPAB,EPAB,DWPI.	17

[There are more results than shown above. Click here to view the entire set.](#)

Display Format:

[Previous Page](#) [Next Page](#)

? b 155, 5

```
12mar02 12:22:00 User242957 Session D407.2
$0.00    0.221 DialUnits File410
$0.00  Estimated cost File410
$0.53  TYMNET
$0.53  Estimated cost this search
$0.53  Estimated total session cost  0.456 DialUnits
```

SYSTEM:OS - DIALOG OneSearch

```
File 155: MEDLINE(R) 1966-2002/Mar W2
File 5: Biosis Previews(R) 1969-2002/Mar W1
(c) 2002 BIOSIS
```

Set Items Description

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```
? s cd(w)81 or tapa(w)1 or cd81 or (target and antiproliferative and antibody and 1)
```

```
89912 CD
123922 81
19 CD(W)81
295 TAPA
5363559 1
217 TAPA(W)1
366 CD81
253723 TARGET
13208 ANTIPROLIFERATIVE
704304 ANTIBODY
5363559 1
S1      524 CD(W)81 OR TAPA(W)1 OR CD81 OR (TARGET AND
ANTIPROLIFERATIVE AND ANTIBODY AND 1)
```

```
? s s1 and (antisens? or ribozym?)
```

```
524 S1
32562 ANTISENS?
5679 RIBOZYM?
S2      3 S1 AND (ANTISENS? OR RIBOZYM?)
```

```
? rd
```

```
...completed examining records
S3      2 RD (unique items)
? t s3/3,ab/all
```

```
3/3,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
```

```
10924028 20363096 PMID: 10907850
Sequence-based structural features between Kvlqtl and Tapal on mouse
chromosome 7F4/F5 corresponding to the Beckwith-Wiedemann syndrome region
on human 11p15.5: long-stretches of unusually well conserved intronic
sequences of kvlqtl between mouse and human.
```

Yatsuki H; Watanabe H; Hattori M; Joh K; Soejima H; Komoda H; Xin Z; Zhu
X; Higashimoto K; Nishimura M; Kuratomi S; Sasaki H; Sakaki Y; Mukai T

Department of Biochemistry, Saga Medical School, Saga, Japan.

DNA research (JAPAN) Jun 30 2000, 7 (3) p195-206, ISSN 1340-2838

Journal Code: CCB

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Mouse chromosome 7F4/F5 is a syntenic locus of human 11p15.5 in which
many imprinted genes are clustered. Transmission of aberrant human 11p15.5
or duplicated 11p causes Beckwith-Wiedemann syndrome (BWS) depending on
which parent the chromosome is derived from. To analyze a syntenic mouse

locus corresponding to human 11p15.5, mouse BAC contigs were constructed between Nap2 and Tap1, in which 390 kb was sequenced between Kvlqtl and Tap1. An unexpected finding was that of highly conserved intronic sequences of Kvlqtl between mouse and human, and their homologies came up to at least 160 kb because the length of this gene extended to 350 kb, suggesting the possibility of some functional constraint due to transcriptional and/or post-transcriptional regulation of this region. Many expressed sequence tags (ESTs) were mapped on this locus. Three genes, Lit1 (Kvlqtl-AS), Mtr1 and Tssc4, were identified and characterized. Lit1 is an **antisense** transcript of Kvlqtl and paternally expressed and maternally methylated throughout the developmental stage. The position where Lit1 exists corresponded to a highly conserved region between mouse and human. This transcript extends at least 60 kb from downstream to upstream of exon 10 in Kvlqtl. Tssc4 and Mtr1 carried putative open reading frames but neither was imprinted. Further characterization of this locus based on the sequence comparison between mouse and human will contribute valuable information towards resolving the mechanism of the occurrence of BWS and the associated childhood tumor.

3/3,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10471384 20117181 PMID: 10653456
Hepatitis C--virology and future antiviral targets.
Di Bisceglie AM

Department of Internal Medicine, Saint Louis University School of Medicine, Missouri 63104, USA.

American journal of medicine (UNITED STATES) Dec 27 1999, 107 (6B)
p45S-48S, ISSN 0002-9343 Journal Code: 3JU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The hepatitis C virus is a single-stranded RNA virus with a genome approximately 9,000 nucleotides in length. The genome consists of a single, large open reading frame (ORF) and 5' and 3' untranslated regions. The highly conserved 5' untranslated region is 341 nucleotides in length with a complex secondary structure and may function as an internal ribosomal entry site (IRES). The 3' untranslated region is approximately 500 nucleotides in length and contains a hypervariable region, followed by a poly(U) sequence and a highly conserved 98-nucleotide element with a stable secondary structure. The ORF codes form a single polyprotein that is processed into as many as 10 polypeptides, including a capsid protein (core), two envelope proteins (E1 and E2), and nonstructural proteins (NS2, NS3, NS4, and NS5). Potentially suitable antiviral targets include the IRES, protease, helicase, and RNA polymerase. In vitro studies show that **antisense** oligonucleotides can inhibit the production of structural HCV proteins and may be therapeutically useful if the problems of stability and delivery can be solved. The binding of HCV envelope proteins to **CD81**, a potential receptor for viral entry into hepatocytes, has recently been described and also raises the possibility of agents to block the binding to **CD81** or the entry of the virus into cells.

? ds

Set	Items	Description
S1	524	CD(W)81 OR TAPA(W)1 OR CD81 OR (TARGET AND ANTIPIROLIFERATIVE AND ANTIBODY AND 1)
S2	3	S1 AND (ANTISENS? OR RIBOZYM?)
S3	2	RD (unique items)

? s s1 and inhibit?

524 S1
1952892 INHIBIT?

S4 133 S1 AND INHIBIT?

? rd

...examined 50 records (50)
...examined 50 records (100)
...completed examining records
S5 82 RD (unique items)
? t s5/3,ab/all

5/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

12921099 21881750 PMID: 11884446
Complement Receptor Type 1 (CD35) Mediates **Inhibitory** Signals in
Human B Lymphocytes.
Jozsi Mihaly; Prechl Jozsef; Bajtay Zsuzsa; Erdei Anna
Department of Immunology and Research Group of the Hungarian Academy of
Sciences, Eotvos Lorand University, Budapest, Hungary.
Journal of immunology (Baltimore, Md. : 1950) (United States) Mar 15
2002, 168 (6) p2782-8, ISSN 0022-1767 Journal Code: 2985117R

Languages: ENGLISH
Document type: Journal Article
Record type: In Process
The complement system--particularly component C3---has been demonstrated to be a key link between innate and adaptive immunity. The trimolecular complex of complement receptor type 2 (CR2), CD19, and **CD81** is known to promote B cell activation when coligated with the B cell Ag receptor. In the present study, we aimed to elucidate the role of human complement receptor type 1 (CR1), the other C3-receptor on B cells. As ligand, aggregated C3 and aggregated C3(H₂O), i.e., multimeric "C3b-like C3", are used, which bind to CR1, but not to CR2. In experiments studying the functional consequences of CR1-clustering, the multimeric ligand is shown to **inhibit** the proliferation of tonsil B cells activated with a suboptimal dose of anti-IgM F(ab')₂. Importantly, this **inhibitory** activity also occurs in the presence of the costimulatory cytokines IL-2 and IL-15. The anti-IgM-induced transient increase in the concentration of intracellular free Ca⁽²⁺⁾ and phosphorylation of several cytoplasmic proteins are strongly reduced in the presence of the CR1 ligand. Data presented indicate that CR1 has a negative regulatory role in the B cell Ag receptor mediated activation of human B lymphocytes.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

12852339 21663948 PMID: 11805134
Primary hepatocytes of *Tupaia belangeri* as a potential model for hepatitis C virus infection.
Zhao Xiping; Tang Zhen-Ya; Klumpp Bettina; Wolff-Vorbeck Guido; Barth Heidi; Levy Shoshana; von Weizsacker Fritz; Blum Hubert E; Baumert Thomas F
Department of Medicine II, University of Freiburg, Freiburg, Germany.
Journal of clinical investigation (United States) Jan 2002, 109 (2)
p221-32, ISSN 0021-9738 Journal Code: 7802877

Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Hepatitis C virus (HCV) is a major cause of chronic hepatitis worldwide, but the study of HCV infection has been hampered by the lack of an in vitro or in vivo small animal model. The tree shrew *Tupaia belangeri* is susceptible to infection with a variety of human viruses in vivo, including hepatitis viruses. We show that primary *Tupaia* hepatocytes can be infected with serum- or plasma-derived HCV from infected humans, as measured by de novo synthesis of HCV RNA, analysis of viral quasispecies evolution, and

detection of viral proteins. Production of infectious virus could be demonstrated by passage to naive hepatocytes. To assess whether viral entry in Tupaia hepatocytes was dependent on the recently isolated HCV E2 binding protein **CD81**, we identified and characterized Tupaia **CD81**. Sequence analysis of cloned Tupaia cDNA revealed a high degree of homology between Tupaia and human **CD81** large extracellular loops (LEL). Cellular binding of E2 and HCV infection could not be **inhibited** by anti-**CD81** antibodies or soluble **CD81**-LEL, suggesting that viral entry can occur through receptors other than **CD81**. Thus, primary Tupaia hepatocytes provide a potential model for the study of HCV infection of hepatocytes.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12832614 21827605 PMID: 11838967

Comparison of adhesion mechanisms and surface protein expression in CD77-positive and CD77-negative Burkitt's lymphoma cells.

Jackson T; Van Exel C; Reagans K; Verret R; Maloney M
Department of Biology, Spelman College, Atlanta, Georgia 30314-4399, USA.
Cellular and molecular biology (Noisy-le-Grand, France) (France) Nov

2001, 47 (7) p1195-200, ISSN 0145-5680 Journal Code: 9216789

Contract/Grant No.: GM08241, GM, NIGMS; RR11598, RR, NCRR

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

The Burkitt lymphoma-derived Daudi cell line is often used as an in vitro model for germinal center B-cell function. Globotriaosyl ceramide (CD77), a marker for germinal center B-cells, is present on Daudi cells but is deficient in the Daudi-derived mutant VT500 cell line. Previous results showed a correlation in these cells between CD77 expression and expression of the B-cell protein CD19 and indicated that CD19/CD77 interaction is a mechanism for B-cell adhesion. Roles for CD77 in IFN-alpha-induced growth **inhibition** and anti-viral activity also have been described previously. Through flow cytometric analysis and adhesion assays, we investigated whether expression of CD77 was required for cell adhesion pathways induced by IFN or antibodies against additional B-cell surface molecules: CD20, CD22, CD38, CD40, **CD81** and HLA-D proteins. In contrast to the pronounced homotypic adhesion induced by treatment with interferon-alpha in Daudi cells, no increase in adhesion was observed in IFN-treated VT500 cells. Of the B-cell proteins tested, only CD22-mediated adhesion and surface expression was stronger in Daudi than in VT500 cells. These results indicate that CD77 may be required for IFN and CD22-associated adhesion pathways, but CD77 is not a universal component of adhesion pathways in these cells.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12831100 21635497 PMID: 11773394

Binding of hepatitis C virus-like particles derived from infectious clone H77C to defined human cell lines.

Wellnitz Sabine; Klumpp Bettina; Barth Heidi; Ito Susumu; Depla Erik;
Dubuisson Jean; Blum Hubert E; Baumert Thomas F

Department of Medicine II, University of Freiburg, Freiburg, Germany.
Journal of virology (United States) Feb 2002, 76 (3) p1181-93,
ISSN 0022-538X Journal Code: 0113724

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Hepatitis C virus (HCV) is a leading cause of chronic hepatitis in the world. The study of viral entry and infection has been hampered by the

inability to efficiently propagate the virus in cultured cells and the lack of a small-animal model. Recent studies have shown that in insect cells, the HCV structural proteins assemble into HCV-like particles (HCV-LPs) with morphological, biophysical, and antigenic properties similar to those of putative virions isolated from HCV-infected humans. In this study, we used HCV-LPs derived from infectious clone H77C as a tool to examine virus-cell interactions. The binding of partially purified particles to human cell lines was analyzed by fluorescence-activated cell sorting with defined monoclonal antibodies to envelope glycoprotein E2. HCV-LPs demonstrated dose-dependent and saturable binding to defined human lymphoma and hepatoma cell lines but not to mouse cell lines. Binding could be **inhibited** by monoclonal anti-E2 antibodies, indicating that the HCV-LP-cell interaction was mediated by envelope glycoprotein E2. Binding appeared to be **CD81** independent and did not correlate with low-density lipoprotein receptor expression. Heat denaturation of HCV-LPs drastically reduced binding, indicating that the interaction of HCV-LPs with target cells was dependent on the proper conformation of the particles. In conclusion, our data demonstrate that insect cell-derived HCV-LPs bind specifically to defined human cell lines. Since the envelope proteins of HCV-LPs are presumably presented in a virion-like conformation, the binding of HCV-LPs to target cells may allow the study of virus-host cell interactions, including the isolation of HCV receptor candidates and antibody-mediated neutralization of binding.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12795471 21640531 PMID: 11781364
Binding of the hepatitis C virus envelope protein E2 to **CD81** **inhibits** natural killer cell functions.

Tseng Chien-Te K; Klimpel Gary R
Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX 77555, USA.

Journal of experimental medicine (United States) Jan 7 2002, 195 (1)
p43-9, ISSN 0022-1007 Journal Code: 2985109R

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Little is known about how this virus is able to persist or whether this persistence might be because of its ability to alter the early innate immune response. The major HCV envelope protein E2 has been shown to bind to **CD81**. Thus, HCV binding to natural killer (NK) cells could result in the cross-linking of **CD81**. To explore this possibility, we investigated whether cross-linking **CD81** on NK cells could alter NK cell function. **CD81** cross-linking by monoclonal antibody (mAb) specific for **CD81** or by immobilized E2 have been shown to result in costimulatory signals for human T cells. In this study, we show that **CD81** cross-linking via immobilized E2 or mAbs specific for **CD81** **inhibits** not only non major histocompatibility complex-restricted cytotoxicity mediated by NK cells but also interferon (IFN)-gamma production by NK cells after exposure to interleukin (IL)-2, IL-12, IL-15, or CD16 cross-linking. These results show that **CD81** cross-linking mediates completely different signals in NK cells versus T cells. Importantly, these results suggest that one mechanism whereby HCV can alter host defenses and innate immunity is via the early **inhibition** of IFN-gamma production by NK cells.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12795470 21640530 PMID: 11781363

Inhibition of natural killer cells through engagement of **CD81** by the major hepatitis C virus envelope protein.

Crotta Stefania; Stillà Annalisa; Wack Andreas; D'Andrea Annalisa; Nuti Sandra; D'Oro Ugo; Mosca Marta; Filippini Franco; Brunetto R Maurizia; Bonino Ferruccio; Abrignani Sergio; Valiante Nicholas M

IRIS, Department of Immunology, Chiron S.p.A., 53100 Siena, Italy.

Journal of experimental medicine (United States) Jan 7 2002, 195 (1) p35-41, ISSN 0022-1007 Journal Code: 2985109R

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The immune response against hepatitis C virus (HCV) is rarely effective at clearing the virus, resulting in approximately 170 million chronic HCV infections worldwide. Here we report that ligation of an HCV receptor (**CD81**) **inhibits** natural killer (NK) cells. Cross-linking of **CD81** by the major envelope protein of HCV (HCV-E2) or anti-**CD81** antibodies blocks NK cell activation, cytokine production, cytotoxic granule release, and proliferation. This **inhibitory** effect was observed using both activated and resting NK cells. Conversely, on NK-like T cell clones, including those expressing NK cell **inhibitory** receptors, **CD81** ligation delivered a costimulatory signal. Engagement of **CD81** on NK cells blocks tyrosine phosphorylation through a mechanism which is distinct from the negative signaling pathways associated with NK cell **inhibitory** receptors for major histocompatibility complex class I. These results implicate HCV-E2-mediated **inhibition** of NK cells as an efficient HCV evasion strategy targeting the early antiviral activities of NK cells and allowing the virus to establish itself as a chronic infection.

5/3,AB/7 (Item 7 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12777448 21668235 PMID: 11809733

Depletion of Lyn kinase from the BCR complex and **inhibition** of B cell activation by excess CD21 ligation.

Chakravarty Leena; Zabel Mark D; Weis Janis J; Weis John H

Division of Cell Biology and Immunology, Department of Pathology, University of Utah, School of Medicine, 50 N. Medical Drive, Salt Lake City, UT 84132, USA.

International immunology (England) Feb 2002, 14 (2) p139-46, ISSN 0953-8178 Journal Code: 8916182

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

The human and murine CD21 gene products have been functionally linked to B cell activation by the co-ligation of the BCR and the CD21/CD19/**CD81** complexes. Binding of low levels of antigen complexed to the complement ligand(s) for CD21 enhances B cell activation compared to the stimulation caused by antigen alone. Mice lacking functional CD21 predispose to autoimmune responses suggesting that this receptor may also play a negative role: thus in the presence of excess complement-bearing immune complexes, B cell antigen-specific activation may be **inhibited**. This possibility was investigated using intracellular calcium elicitation analyses to follow BCR-mediated activation. Ligation of the BCR and limiting quantities of the CD21 receptor demonstrated the expected enhanced cellular response compared to BCR ligation alone: CD21 ligation alone demonstrated no alteration in calcium flux. However, co-ligation of the BCR with excess CD21 binding resulted in the elimination of the calcium response, suggesting that CD21 ligation was down-modulating the BCR response. Immunoprecipitation of kinases associated with the BCR and CD21/CD19/**CD81** complexes demonstrated that Lyn is preferentially depleted from the BCR complex following excess binding of CD21. Localization of other kinases integral for B cell activation is not

altered. These data suggest that excess CD21 ligand binding can negatively impact B cell activation by sequestering Lyn kinase away from the BCR complex.

5/3,AB/8 (Item 8 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12767778 21663975 PMID: 11805154

Murine CD9 Is the Receptor for Pregnancy-specific Glycoprotein 17.
Waterhouse Roseann; Ha Cam; Dveksler Gabriela S
Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814.

Journal of experimental medicine (United States) Jan 21 2002, 195 (2) p277-82, ISSN 0022-1007 Journal Code: 2985109R

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

Pregnancy-specific glycoproteins (PSGs) are a family of highly similar secreted proteins produced by the placenta. PSG homologs have been identified in primates and rodents. Members of the human and murine PSG family induce secretion of antiinflammatory cytokines in mononuclear phagocytes. For the purpose of cloning the receptor, we screened a RAW 264.7 cell cDNA expression library. The PSG17 receptor was identified as the tetraspanin, CD9. We confirmed binding of PSG17 to CD9 by ELISA, flow cytometry, alkaline phosphatase binding assays, and *in situ* rosetting. Anti-CD9 monoclonal antibody inhibited binding of PSG17 to CD9-transfected cells and RAW 264.7 cells. Moreover, PSG17 binding to macrophages from CD9-deficient mice was significantly reduced. We then tested whether PSG17 binds to other members of the murine tetraspanin family. PSG17 did not bind to cells transfected with CD53, CD63, CD81, CD82, or CD151, suggesting that PSG17-CD9 binding is a specific interaction. We have identified the first receptor for a murine PSG as well as the first natural ligand for a member of the tetraspanin superfamily.

5/3,AB/9 (Item 9 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

12693122 21634773 PMID: 11773042

Retinal Pigment Epithelium of the Rat Express CD81, the Target of the Anti-proliferative Antibody (TAPA).

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Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee.

Investigative ophthalmology & visual science (United States) Jan 2002, 43 (1) p274-80, ISSN 0146-0404 Journal Code: 7703701

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

PURPOSE. The present study focuses on the role of CD81, the target of the anti-proliferative antibody (TAPA), in the regulation of the growth of retinal pigment epithelium (RPE). METHODS. RPE of 8-day-old rat pups was cultured. The level of CD81 in the cultures was defined by immunoblot methods, and the distribution of the protein was examined using indirect immunohistochemical methods. In addition, the effects of the antibody binding were tested in culture. RESULTS. CD81 was found in all layers of the normal retina with a distinct absence of labeling in the inner and outer segments of the photoreceptors. Based on the authors' original immunohistochemical analysis, it was difficult to determine whether CD81 was expressed by RPE. By examining cultures of RPE it was demonstrated that CD81 was expressed on the surface of these cells and that it was concentrated at regions of cell-cell contact. Indirect immunohistochemical methods using a peroxidase-labeled secondary antibody

in albino mice revealed heavy labeling of the RPE in the intact eye. When the AMP1 antibody (directed against the large extracellular loop of **CD81**) was added to cultured RPE, the mitotic activity of the cells was depressed. CONCLUSIONS. **CD81** was found in the normal rat retina. Previous studies demonstrated that **CD81** was expressed in retinal glia, the Muller cells that span the thickness of the retina, and astrocytes found in the ganglion cell layer. The present study demonstrated that **CD81** was also expressed by RPE. The dramatic effects of the AMP1 antibody and the location of **CD81** at regions of cell-cell contact support the hypothesis that this molecule is part of a molecular switch controlling contact **inhibition**.

5/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12643065 21599742 PMID: 11739177

Regulatory role of tetraspanin CD9 in tumor-endothelial cell interaction during transendothelial invasion of melanoma cells.

Longo N; Yanez-Mo M; Mittelbrunn M; de la Rosa G; Munoz M L;
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Blood (United States) Dec 15 2001, 98 (13) p3717-26, ISSN 0006-4971
Journal Code: 7603509

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

Heterotypic interaction among tumor cells (TCs) and endothelial cells (ECs) may play a critical role during the vascular dissemination of neoplastic cells and during pathologic angiogenesis in tumors. To identify molecules involved in these processes, the distribution of vascular junctional proteins was first studied by immunofluorescence at sites of heterologous intercellular contact using TC-EC mosaic monolayers grown on 2-dimensional collagen. Several members of the tetraspanin superfamily, including CD9, **CD81**, and CD151, were found to localize at the TC-EC contact area. The localization of tetraspanins to the TC-EC heterologous contact area was also observed during the active transmigration of TCs across EC monolayers grown onto 3-dimensional collagen matrices. Dynamic studies by time-lapse immunofluorescence confocal microscopy showed an active redistribution of endothelial CD9 to points of melanoma insertion. Anti-CD9 monoclonal antibodies were found to specifically **inhibit** the transendothelial migration of melanoma cells; the **inhibitory** effect was likely caused by a strengthening of CD9-mediated heterotypic interactions of TCs to the EC monolayer. These data support a novel mechanism of tetraspanin-mediated regulation of TC transcellular migration independent of TC motility and growth during metastasis and a role for these molecules in the formation of TC-EC mosaic monolayers during tumor angiogenesis.

5/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11786045 21542910 PMID: 11685799

In search of hepatitis C virus receptor(s).

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Clinics in liver disease (United States) Nov 2001, 5 (4) p873-93,
ISSN 1089-3261 Journal Code: DW6

Contract/Grant No.: CA34233, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

Since the genomic sequence of HCV was determined, significant progress has been made towards understanding the functions of the HCV-encoded proteins, despite the lack of an efficient in-vitro replication system or convenient small-animal model. The identity of the receptor for HCV remains elusive, however. Low-density lipoprotein receptor, **CD81**, and GAGs may all act as receptors for HCV, either sequentially or by different viral quasispecies. Recent work using pseudotypic VSV bearing E1 or E2 chimeric molecules showed that entry of the E1 pseudotype can be **inhibited** by recombinant LDLr, whereas the E2 pseudotype is more sensitive to **inhibition** by recombinant **CD81** or heparin. These results suggest that E1 and E2 may be responsible for interactions with different cellular molecules. It is also conceivable that additional, yet unidentified, cellular proteins are involved in viral binding and entry. Intriguingly, the reports of HCV-RNA associated with PBMC suggest that HCV infection may not be restricted to hepatocytes. Thus, separate reservoirs of virus may exist, and HCV may use different receptors to access these different cell types.

5/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

11714929 21471950 PMID: 11588022

The dynamics of hepatitis C virus binding to platelets and 2 mononuclear cell lines.

Hamaia S; Li C; Allain JP

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Blood (United States) Oct 15 2001, 98 (8) p2293-300, ISSN 0006-4971
Journal Code: A8G

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

Hepatitis C virus (HCV) binds to platelets in chronically infected patients where free HCV constitutes only about 5% of total circulating virus. Free HCV preferentially binds to human mononuclear cell lines but free and complexed virus binds equally to platelets. The extent of free HCV binding to human Molt-4 T cells (which express **CD81**) and to human promonocytic U937 cells or to platelets (which do not express **CD81**) was similar. The binding of free HCV to the cell lines was saturated at a virus dose of 1 IU HCV RNA per cell but binding to platelets was not saturable. Human anti-HCV IgG, but not anti-**CD81**, markedly **inhibited** HCV binding to target cells in a dose-dependent manner. Human antibodies to HCV hypervariable region 1 of E2 glycoprotein partially **inhibited** viral binding to target cells. Recombinant E2 also **inhibited** viral binding to target cells in a dose-dependent manner, with the efficacy of this decreasing in the rank order of Molt-4 cells more than U937 cells more than platelets. In contrast to HCV, recombinant E2 bound to Molt-4 cells to an extent markedly greater than that apparent with U937 cells or platelets. These results suggest that the binding of HCV to blood cells is mediated by multiple cell surface receptors and that recombinant E2 binding may not be representative of the interaction of the intact virus with target cells. (Blood. 2001;98:2293-2300)

5/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

11556461 21351041 PMID: 11457993

Functional analysis of hepatitis C virus E2 glycoproteins and virus-like particles reveals structural dissimilarities between different forms of E2.

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Journal of general virology (England) Aug 2001, 82 (Pt 8) p1877-83,
ISSN 0022-1317 Journal Code: I9B

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Structure-function analysis of the hepatitis C virus (HCV) envelope glycoproteins, E1 and E2, has been difficult due to the unavailability of HCV virions. Truncated soluble forms of E2 have been used as models to study virus interaction with the putative HCV receptor **CD81**, but they may not fully mimic E2 structures on the virion. Here, we compared the **CD81**-binding characteristics of truncated E2 (E2(660)) and full-length (FL) E1E2 complex expressed in mammalian cells, and of HCV virus-like particles (VLPs) generated in insect cells. All three glycoprotein forms interacted with human **CD81** in an in vitro binding assay, allowing us to test a panel of well-characterized anti-E2 monoclonal antibodies (MAbs) for their ability to **inhibit** the glycoprotein-**CD81** interaction. MAbs specific for E2 amino acid (aa) regions 396-407, 412-423 and 528-535 blocked binding to **CD81** of all antigens tested. However, MAbs specific for regions 432-443, 436-443 and 436-447 **inhibited** the interaction of VLPs, but not of E2(660) or the FL E1E2 complex with **CD81**, indicating the existence of structural differences amongst the E2 forms. These findings underscore the need to carefully select an appropriate ligand for structure-function analysis.

5/3,AB/14 (Item 14 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

11463011 21184639 PMID: 11288107

VX-497: a novel, selective IMPDH **inhibitor** and immunosuppressive agent.

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Journal of pharmaceutical sciences (United States) May 2001, 90 (5) p625-37, ISSN 0022-3549 Journal Code: JO7

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Inosine monophosphate dehydrogenase (IMPDH) is an essential rate-limiting enzyme in the purine metabolic pathway, catalyzing the de novo synthesis of guanine nucleotides required for lymphocyte proliferation. IMPDH has therefore been an attractive **target** for developing immunosuppressive drugs (e.g., CellCept and mizoribine). Here we describe the immunosuppressive activity of VX-497, a novel noncompetitive **inhibitor** of IMPDH. VX-497 (MW 452.5) is orally bioavailable and **inhibits** the proliferation of primary human, mouse, rat, and dog lymphocytes at concentrations of approximately 100 nM. The **inhibitory** effect of VX-497 on lymphocytes is reversed in the presence of exogenous guanosine, but not in the presence of adenosine or uridine, confirming that the antilymphocytic activity of VX-497 is specifically due to **inhibition** of IMPDH. The **antiproliferative** effect of VX-497 in cells is also reversed within 48 h of its removal. Based on evaluation of VX-497 in several lymphoid and nonlymphoid cells, the **antiproliferative** effect of VX-497 is observed to be most pronounced on lymphoid and keratinocyte cells as compared with fibroblasts. In vivo, oral administration of VX-497 **inhibits** the primary IgM **antibody** response in a dose-dependent manner, with an ED₅₀ value of approximately 30-35 mg/kg in mice. Single daily dosing of VX-497 is observed to be as effective as twice-daily dosing in this model of immune activation. These studies demonstrate that VX-497 is a potent, specific, and reversible IMPDH **inhibitor** that selectively **inhibits** lymphocyte proliferation.

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5/3,AB/15 (Item 15 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

11438797 21191851 PMID: 11294888

Sequence-specific interaction between the disintegrin domain of mouse ADAM 3 and murine eggs: role of betal integrin-associated proteins CD9, CD81, and CD98.

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Molecular biology of the cell (United States) Apr 2001; 12 (4): p809-20, ISSN 1059-1524 Journal Code: BAU

Contract/Grant No.: GM-48739, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

ADAM 3 is a sperm surface glycoprotein that has been implicated in sperm-egg adhesion. Because little is known about the adhesive activity of ADAMs, we investigated the interaction of ADAM 3 disintegrin domains, made in bacteria and in insect cells, with murine eggs. Both recombinant proteins inhibited sperm-egg binding and fusion with potencies similar to that which we recently reported for the ADAM 2 disintegrin domain. Alanine scanning mutagenesis revealed a critical importance for the glutamine at position 7 of the disintegrin loop. Fluorescent beads coated with the ADAM 3 disintegrin domain bound to the egg surface. Bead binding was inhibited by an authentic, but not by a scrambled, peptide analog of the disintegrin loop. Bead binding was also inhibited by the function-blocking anti-alpha6 monoclonal antibody (mAb) GoH3, but not by a nonfunction blocking anti-alpha6 mAb, or by mAbs against either the alpha $\text{\textgreek}{\text{\textalpha}}$ or beta \textbeta integrin subunits. We also present evidence that in addition to the tetraspanin CD9, two other betal-integrin-associated proteins, the tetraspanin CD81 as well as the single pass transmembrane protein CD98 are expressed on murine eggs. Antibodies to CD9 and CD98 inhibited in vitro fertilization and binding of the ADAM 3 disintegrin domain. Our findings are discussed in terms of the involvement of multiple sperm ADAMs and multiple egg betal integrin-associated proteins in sperm-egg binding and fusion. We propose that an egg surface "tetraspan web" facilitates fertilization and that it may do so by fostering ADAM-integrin interactions.

5/3,AB/16 (Item 16 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

11377641 21179883 PMID: 11282207

Immunogenicity of the E1E2 proteins of hepatitis C virus expressed by recombinant adenoviruses.

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Vaccine (England) Apr 6 2001; 19 (20-22) p2955-64, ISSN 0264-410X
Journal Code: X60

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The E1 and E2 proteins of hepatitis C virus (HCV) are believed to be the viral envelope glycoproteins that are major candidate antigens for HCV vaccine development. We reported previously that the replication-competent recombinant adenovirus encoding core-E1-E2 genes of HCV (Ad/HCV) produces serologically reactive E1 and E2 proteins forming a heterodimer in

substantial amounts. Here, we examined immunogenicity of the E1E2 proteins copurified from HeLa cells infected with Ad/HCV virus in mice. Furthermore, we constructed a replication-defective recombinant adenovirus encoding the core-E1-E2 genes of HCV (Ad.CMV.HCV) and examined immunogenicity of the virus in mice. The mice immunized intraperitoneally with the copurified E1E2 proteins induced mainly antibodies to E2, but not to E1 by Western blot analysis. The sera of mice immunized with the E1E2 **inhibited** the binding of E2 protein to the major extracellular loop of human **CD81**. E2-specific cytotoxic T cells (CTLs), but not antibodies to the E1E2 antigens were induced in the mice intramuscularly immunized with Ad.CMV.HCV virus. When immunized with both Ad.CMV.HCV virus and the E1E2, mice elicited E2-specific CTLs and antibodies to the E1E2 antigens. The results suggest that immunization of Ad.CMV.HCV virus combined with E2 protein is an effective modality to induce humoral as well as cellular immune response to E2 antigen.

5/3,AB/17 (Item 17 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

11175452 21024321 PMID: 11149601

Inhibition of mitogen-activated protein kinase kinase selectively **inhibits** cell proliferation in human breast cancer cells displaying enhanced insulin-like growth factor I-mediated mitogen-activated protein kinase activation.

Hermanto U; Zong CS; Wang LH
Department of Microbiology, Mount Sinai School of Medicine, New York, New York 10029-6574, USA.

Cell growth & differentiation (United States) Dec 2000, 11 (12) p655-64, ISSN 1044-9523 Journal Code: AYH
Contract/Grant No.: CA29339, CA, NCI; CA55054, CA, NCI; T32GM07280, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Mitogen-activated protein (MAP) kinase mediates cell proliferation, cell differentiation, and cell survival by regulating signaling pathways activated by receptor protein tyrosine kinases (RPTKs), including the insulin-like growth factor 1 receptor (IGF-IR). We analyzed the upstream signaling components of the MAP kinase pathway, including RPTKs, in human breast cancer cell lines and found that some of those components were overexpressed. Importantly, signaling molecules such as IGF-IR, insulin receptor, and insulin receptor substrate 1, leading to the MAP kinase pathway, were found to be concomitantly overexpressed within certain tumor lines, i.e., MCF-7 and T-47D. When compared with the nonmalignant and other breast tumor lines examined, MCF-7 and T-47D cells displayed a more rapid, robust, and sustained MAP kinase activation in response to insulin-like growth factor I (IGF-I) stimulation. By contrast, IGF-I treatment led to a sustained down-regulation of MAP kinase in those lines overexpressing Erbb2-related RPTKs. Interestingly, blocking the MAP kinase pathway with PD098059 had the greatest **antiproliferative** effect on MCF-7 and T-47D among the normal and tumor lines tested. Furthermore, addition of an IGF-IR blocking **antibody** to growth medium attenuated the ability of PD098059 to suppress the growth of MCF-7 and T-47D cells. Thus, our study suggests that concomitant overexpression of multiple signaling components of the IGF-IR pathway leads to the amplification of IGF-I-mediated MAP kinase signaling and resultant sensitization to PD098059. The enhanced sensitivity to PD098059 implies an increased requirement for the MAP kinase pathway in those breast cancer cells, making this pathway a potential **target** in the treatment of selected breast malignancies.

5/3,AB/18 (Item 18 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

11149519 21178593 PMID: 11282549

The hepatitis C virus (HCV) induces a long-term increase in interleukin-10 production by human CD4+ T cells (H9).

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European cytokine network (France) Mar 2001, 12 (1) p69-77, ISSN

1148-5493 Journal Code: A56

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

Patients with chronic hepatitis C present an imbalance of Th1/Th2 cytokine production. Therefore, we investigated whether the exposure of the CD4+ T cell line H9 to HCV could induce activation of cells through synthesis of IL-10. Three infection protocols were performed to enhance HCV propagation. Viral particles were prepared by ultracentrifugation of serum from patients. From 3 to 81 days post-infection (p.i.), HCV-RNA was monitored both in supernatants and cells by nested RT-PCR, IL-10 protein in medium by ELISA, and IL-10 mRNA in cells by semi-quantitative RT-PCR. The expression of tetraspanins was analyzed by flow cytometry. The PKC signal pathway was studied using specific **inhibitors**. The H9 cells express **CD81**. HCV-RNA (+) was detected in cells until 21 days p.i., and in culture media over 39 days p.i. Up to day 81 p.i., HCV exposure induced a specific, 2-fold increase of IL-10 production by H9 cells. IL-10 production was **inhibited** by a PKC **inhibitor** (Calphostin C). This study shows that even if the infection of H9 T cells did not result in any viral progeny, HCV induced the activation of IL-10 secretion, which supports the role of IL-10 in HCV pathogenesis.

5/3,AB/19 (Item 19 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

11139195 21100417 PMID: 11167010

The zebrafish fth1, slc3a2, men1, pc, fgf3 and cycd1 genes define two regions of conserved synteny between linkage group 7 and human chromosome 11q13.

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Gene (Netherlands) Dec 31 2000, 261 (2) p235-42, ISSN 0378-1119

Journal Code: FOP

Contract/Grant No.: GM30321, GM, NIGMS; R37 AI23338, AI, NIAID

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

In addition to being an excellent model system for studying vertebrate development, the zebrafish has become a great tool for gene discovery by mutational analysis. The recent availability of the zebrafish EST database and radiation hybrid mapping panels has dramatically expanded the framework for genomic research in this species. Developing comparative maps of the zebrafish and human genomes is of particular importance for zebrafish mutagenesis studies in which human orthologs are sought for zebrafish genes. However, only partial cDNA sequences are determined routinely for mapped ESTs, leaving the identity of the EST in question. It previously had been reported that zebrafish linkage group 7 shares conserved synteny with human chromosome 11q13. In an effort to further define this relationship, five full-length zebrafish cDNAs, fth1, slc3a2, prkri, **cd81**, and pc, as well as one putative human gene, DBX were identified and their map positions ascertained. These six genes, along with men1, fgf3 and cycd1 define two regions of conserved synteny between linkage group 7 and 11q13.

5/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10850800 20501110 PMID: 11046035

Allergen-induced airway hyperreactivity is diminished in **CD81**-deficient mice.

Deng J; Yeung VP; Tsitoura D; DeKruyff RH; Umetsu DT; Levy S
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Journal of immunology (UNITED STATES) Nov 1 2000, 165 (9) p5054-61,
ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI37219, AI, NIAID; AI45900, AI, NIAID; CA34233, CA, NCI; +

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We demonstrated previously that **CD81**(-/-) mice have an impaired Th2 response. To determine whether this impairment affected allergen-induced airway hyperreactivity (AHR), **CD81**(-/-) BALB/c mice and **CD81**(+/+) littermates were sensitized i.p. and challenged intranasally with OVA. Although wild type developed severe AHR, **CD81**(-/-) mice showed normal airway reactivity and reduced airway inflammation. Nevertheless, OVA-specific T cell proliferation was similar in both groups of mice. Analysis of cytokines secreted by the responding **CD81**(-/-) T cells, particularly those derived from peribronchial draining lymph nodes, revealed a dramatic reduction in IL-4, IL-5, and IL-13 synthesis. The decrease in cytokine production was not due to an intrinsic T cell deficiency because naive **CD81**(-/-) T cells responded to polyclonal Th1 and Th2 stimulation with normal proliferation and cytokine production. Moreover, there was an increase in T cells and a decrease in B cells in peribronchial lymph nodes and in spleens of immunized **CD81**(-/-) mice compared with wild-type animals. Interestingly, OVA-specific Ig levels, including IgE, were similar in **CD81**(-/-) and **CD81**(+/+) mice. Thus, **CD81** plays a role in the development of AHR not by influencing Ag-specific IgE production but by regulating local cytokine production.

5/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10848160 20499063 PMID: 11044085

Human monoclonal antibodies that inhibit binding of hepatitis C virus E2 protein to **CD81** and recognize conserved conformational epitopes.

Hadlock KG; Lanford RE; Perkins S; Rowe J; Yang Q; Levy S; Pileri P; Abrignani S; Foung SK

Departments of Pathology, Stanford University, Stanford, CA 94304, USA.
Journal of virology (UNITED STATES) Nov 2000, 74 (22) p10407-16,
ISSN 0022-538X Journal Code: KCV

Contract/Grant No.: AI40035, AI, NIAID; DA-06596, DA, NIDA; HL-33811, HL, NHLBI; +

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The intrinsic variability of hepatitis C virus (HCV) envelope proteins E1 and E2 complicates the identification of protective antibodies. In an attempt to identify antibodies to E2 proteins from divergent HCV isolates, we produced HCV E2 recombinant proteins from individuals infected with HCV genotypes 1a, 1b, 2a, and 2b. These proteins were then used to characterize 10 human monoclonal antibodies (HMabs) produced from peripheral B cells isolated from an individual infected with HCV genotype 1b. Nine of the antibodies recognize conformational epitopes within HCV E2. Six HMabs

identify epitopes shared among HCV genotypes 1a, 1b, 2a, and 2b. Six, including five broadly reactive HMabs, could inhibit binding of HCV E2 of genotypes 1a, 1b, 2a, and 2b to human CD81 when E2 and the antibody were simultaneously exposed to CD81. Surprisingly, all of the antibodies that inhibited the binding of E2 to CD81 retained the ability to recognize preformed CD81-E2 complexes generated with some of the same recombinant E2 proteins. Two antibodies that did not recognize preformed complexes of HCV 1a E2 and CD81 also inhibited binding of HCV 1a virions to CD81. Thus, HCV-infected individuals can produce antibodies that recognize conserved conformational epitopes and inhibit the binding of HCV to CD81. The inhibition is mediated via antibody binding to epitopes outside of the CD81 binding site in E2, possibly by preventing conformational changes in E2 that are required for CD81 binding.

5/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10848096 20481645 PMID: 11024134

Characterization of hepatitis C virus (HCV) and HCV E2 interactions with CD81 and the low-density lipoprotein receptor.

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Journal of virology (UNITED STATES) Nov 2000, 74 (21) p10055-62,
ISSN 0022-538X Journal Code: KCV

Contract/Grant No.: KO8 A101460, PHS; R01 AA12671, AA, NIAAA

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Hepatitis C virus (HCV) or HCV-low-density lipoprotein (LDL) complexes interact with the LDL receptor (LDLr) and the HCV envelope glycoprotein E2 interacts with CD81 in vitro. However, E2 interactions with LDLr and HCV interactions with CD81 have not been clearly described. Using sucrose gradient-purified low-density particles (1.03 to 1.07 g/cm³), intermediate-density particles (1.12 to 1.18 g/cm³), recombinant E2 protein, or control proteins, we assessed binding to MOLT-4 cells, foreskin fibroblasts, or LDLr-deficient foreskin fibroblasts at 4 degrees C by flow cytometry and confocal microscopy. Viral entry was determined by measuring the coentry of alpha-sarcin, a protein synthesis inhibitor. We found that low-density HCV particles, but not intermediate-density HCV or controls bound to MOLT-4 cells and fibroblasts expressing the LDLr. Binding correlated with the extent of cellular LDLr expression and was inhibited by LDL but not by soluble CD81. In contrast, E2 binding was independent of LDLr expression and was inhibited by human soluble CD81 but not mouse soluble CD81 or LDL. Based on confocal microscopy, we found that low-density HCV particles and LDL colocalized on the cell surface. The addition of low-density HCV but not intermediate-density HCV particles to MOLT-4 cells allowed coentry of alpha-sarcin, indicating viral entry. The amount of viral entry also correlated with LDLr expression and was independent of the CD81 expression. Using a solid-phase immunoassay, recombinant E2 protein did not interact with LDL. Our data indicate that E2 binds CD81; however, virus particles utilize LDLr for binding and entry. The specific mechanism by which HCV particles interact with LDL or the LDLr remains unclear.

5/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10842886 20478072 PMID: 11022009

Functional features of hepatitis C virus glycoproteins for pseudotype virus entry into mammalian cells.

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Missouri 63110, USA.
Virology (UNITED STATES) Oct 10 2000, 276 (1) p214-26, ISSN
0042-6822 Journal Code: XEA
Contract/Grant No.: AI45250, AI, NIAID; DK58023, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We have previously reported the generation of pseudotype virus from chimeric gene constructs encoding the ectodomain of the E1 or E2 glycoprotein of hepatitis C virus (HCV) genotype 1a appended to the trans membrane domain and cytoplasmic tail of the vesicular stomatitis virus (VSV) G protein. Sera derived from chimpanzees immunized with homologous HCV glycoproteins neutralized pseudotype virus infectivity (L. M. Lagging et al., J. Virol. 72, 3539-3546, 1998). We have now extended this study to further understand the role of HCV glycoproteins in pseudotype virus entry. Although a number of mammalian epithelial cells were susceptible to VSV/HCV pseudotype virus infection, plaquing efficiency was different among host cell lines. Pseudotype virus adsorption at low temperature decreased plaque numbers. Treatment of E1 or E2 pseudotype virus in media between pH 5 and 8 before adsorption on cells did not significantly reduce plaque numbers. On the other hand, treatment of cells with lysosomotropic agents or **inhibitors** of vacuolar H(+) ATPases had an **inhibitory** role on virus entry. Concanavalin A, a plant lectin, exhibited neutralization of both HCV E1 and E2 pseudotype virus infectivity. However, mannose binding protein, a C-type mammalian lectin, did not neutralize virus in the absence or presence of serum complement. Pseudotype virus infectivity was only partially **inhibited** by heparin, a highly sulfated glycosaminoglycan, in a saturable manner. Additional studies suggested that low-density lipoprotein receptor related molecules partially **inhibit** E1 pseudotype virus infectivity, while **CD81** related molecules interfere with E2 pseudotype virus infectivity. A further understanding of HCV entry and strategies appropriate for mimicking cell surface molecules may help in the development of new therapeutic modalities against HCV infection.

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5/3,AB/24 (Item 24 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10842059 20451111 PMID: 10993933

Recombinant human monoclonal antibodies against different conformational epitopes of the E2 envelope glycoprotein of hepatitis C virus that **inhibit** its interaction with **CD81**.

Allander T; Drakenberg K; Beyene A; Rosa D; Abrignani S; Houghton M; Widell A; Grillner L; Persson MA

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Journal of general virology (ENGLAND) Oct 2000, 81 Pt 10 p2451-9,
ISSN 0022-1317 Journal Code: I9B

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The antibody response to the envelope proteins of hepatitis C virus (HCV) may play an important role in controlling the infection. To allow molecular analyses of protective antibodies, we isolated human monoclonal antibodies to the E2 envelope glycoprotein of HCV from a combinatorial Fab library established from bone marrow of a chronically HCV-infected patient. Anti-E2 reactive clones were selected using recombinant E2 protein. The bone marrow donor carried HCV genotype 2b, and E2 used for selection was of genotype 1a. The antibody clones were expressed as Fab fragments in *E. coli*, and as Fab fragments and IgG1 in CHO cells. Seven different antibody clones were

characterized, and shown to have high affinity for E2, genotype 1a. Three clones also had high affinity for E2 of genotype 1b. They all bind to conformation-dependent epitopes. Five clones compete for the same or overlapping binding sites, while two bind to one or two other epitopes of E2. Four clones corresponding to the different epitopes were tested as purified IgG1 for blocking the **CD81**-E2 interaction in vitro; all four were positive at 0.3-0.5 microg/ml. Thus, the present results suggest the existence of at least two conserved epitopes in E2 that mediate inhibition of the E2-**CD81** interaction, of which one appeared immunodominant in this donor.

5/3,AB/25 (Item 25 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10777246 20267869 PMID: 10806098

Transmembrane-4-superfamily proteins CD151 and **CD81** associate with alpha 3 beta 1 integrin, and selectively contribute to alpha 3 beta 1-dependent neurite outgrowth.

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Journal of cell science (ENGLAND) Jun 2000, 113 (Pt 11) p1871-82,
ISSN 0021-9533 Journal Code: HNK

Contract/Grant No.: GM38903, GM, NIGMS; NS10344, NS, NINDS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Proteins in the transmembrane-4-superfamily (TM4SF) form many different complexes with proteins in the integrin family, but the functional utility of these complexes has not yet been demonstrated. Here we show that TM4SF proteins CD151, **CD81**, and CD63 co-distribute with alpha3beta1 integrin on neurites and growth cones of human NT2N cells. Also, stable CD151-alpha3beta1 and **CD81**-alpha3beta1 complexes were recovered in NT2N detergent lysates. Total NT2N neurite outgrowth on laminin-5 (a ligand for alpha3beta1 integrin) was strongly inhibited by anti-CD151 and -**CD81** antibodies either together (approximately 85% inhibition) or alone (approximately 45% inhibition). Notably, these antibodies had no inhibitory effect on NT2N neurites formed on laminin-1 or fibronectin, when alpha3beta1 integrin was not engaged. Neurite number, length, and rate of extension were all affected by anti-TM4SF antibodies. In summary: (1) these substrate-dependent inhibition results strongly suggest that CD151 and **CD81** associations with alpha3beta1 are functionally relevant, (2) TM4SF proteins CD151 and **CD81** make a strong positive contribution toward neurite number, length, and rate of outgrowth, and (3) NT2N cells, a well-established model of immature central nervous system neurons, can be a powerful system for studies of integrin function in neurite outgrowth and growth cone motility.

5/3,AB/26 (Item 26 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10716942 20384781 PMID: 10925271

CD81 and CD28 costimulate T cells through distinct pathways.

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Journal of immunology (UNITED STATES) Aug 15 2000, 165 (4) p1902-9,
ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI32751, AI, NIAID; AI40616, AI, NIAID

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We have examined the role of **CD81** in the activation of murine splenic alphabeta T cells. Expression of the **CD81** molecule on T cells increases following activation, raising the possibility of a role for this molecule in progression of the activation process. Using an in vitro costimulation assay, we show that **CD81** can function as a costimulatory molecule on both CD4+ and CD8+ T cells. This costimulation functions independently of CD28, and unlike costimulation through CD28, is susceptible to **inhibition** by cyclosporin A. Strikingly, the pattern of cytokine production elicited by costimulation via **CD81** is unique. IL-2 production was not up-regulated, whereas both IFN-gamma and TNF-alpha expression significantly increased. Together our results demonstrate an alternate pathway for costimulation of T cell activation mediated by **CD81**.

5/3,AB/27 (Item 27 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10687854 20351724 PMID: 10891408

Hepatitis C virus glycoprotein E2 binding to **CD81**: the role of E1E2 cleavage and protein glycosylation in bioactivity.

Chan-Fook C; Jiang WR; Clarke BE; Zitzmann N; Maidens C; McKeating JA; Jones IM

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Virology (UNITED STATES) Jul 20 2000, 273 (1) p60-6, ISSN 0042-6822
Journal Code: XEA

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The hepatitis C virus glycoproteins E1 and 2 have been expressed using recombinant baculoviruses following fusion to the carrier protein glutathione S-transferase (GST). Proteins were expressed singly and as an E1E2 polyprotein with and without an N-terminal affinity tag. Expression of the E1E2 polyprotein, even when preceded by GST, led to processing in insect cells and detection of an E1E2 complex that could be specifically purified by glutathione affinity chromatography. Baculovirus expressed E2 and a purified GST-E1E2 protein bound to the second extracellular loop of **CD81** (EC2), a reported ligand for the molecule, but not to a truncated derivative of **CD81** consisting of only the central domain of the loop. Purified GST-E2, however, failed to bind to **CD81** suggesting a requirement for a free E2 amino terminus for biological activity. The binding to **CD81** by baculovirus expressed E2 protein was comparable to that observed for E2 derived from mammalian cells when detected by a monoclonal antibody sensitive to protein conformation. Furthermore, E2 protein expressed in insect cells in the presence of N-butyldeoxyojirimycin, an **inhibitor** of terminal glucose residue processing, formed complexes with E1 and bound to **CD81**-EC2 similarly to untreated protein. Together these data suggest that although hyperglucosylation of E2 does not have a major effect on bioactivity, polyprotein processing to reveal the free amino terminus is required.
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5/3,AB/28 (Item 28 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10676589 20347351 PMID: 10888628

Evaluation of hepatitis C virus glycoprotein E2 for vaccine design: an endoplasmic reticulum-retained recombinant protein is superior to secreted recombinant protein and DNA-based vaccine candidates.

Heile JM; Fong YL; Rosa D; Berger K; Saletti G; Campagnoli S; Bensi G; Capo S; Coates S; Crawford K; Dong C; Wninger M; Baker G; Cousens L; Chien D; Ng P; Archangel P; Grandi G; Houghton M; Abrignani S

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Journal of virology (UNITED STATES) Aug 2000, 74 (15) p6885-92,
ISSN 0022-538X Journal Code: KCV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Hepatitis C virus (HCV) is the leading causative agent of blood-borne chronic hepatitis and is the target of intensive vaccine research. The virus genome encodes a number of structural and nonstructural antigens which could be used in a subunit vaccine. The HCV envelope glycoprotein E2 has recently been shown to bind **CD81** on human cells and therefore is a prime candidate for inclusion in any such vaccine. The experiments presented here assessed the optimal form of HCV E2 antigen from the perspective of antibody generation. The quality of recombinant E2 protein was evaluated by both the capacity to bind its putative receptor **CD81** on human cells and the ability to elicit antibodies that inhibited this binding (NOB antibodies). We show that truncated E2 proteins expressed in mammalian cells bind with high efficiency to human cells and elicit NOB antibodies in guinea pigs only when purified from the core-glycosylated intracellular fraction, whereas the complex-glycosylated secreted fraction does not bind and elicits no NOB antibodies. We also show that carbohydrate moieties are not necessary for E2 binding to human cells and that only the monomeric nonaggregated fraction can bind to **CD81**. Moreover, comparing recombinant intracellular E2 protein to several E2-encoding DNA vaccines in mice, we found that protein immunization is superior to DNA in both the quantity and quality of the antibody response elicited. Together, our data suggest that to elicit antibodies aimed at blocking HCV binding to **CD81** on human cells, the antigen of choice is a mammalian cell-expressed, monomeric E2 protein purified from the intracellular fraction.

5/3,AB/29 (Item 29 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10651513 20304866 PMID: 10844555

Tetraspanins are localized at motility-related structures and involved in normal human keratinocyte wound healing migration.

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Journal of investigative dermatology (UNITED STATES) Jun 2000, 114 (6) p1126-35, ISSN 0022-202X Journal Code: IHZ

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We have described previously that betal integrins, which mediate keratinocyte cell adhesion and migration, are in ligand-occupied conformation at the basal surface but not at the lateral and apical surfaces of keratinocytes. This led us to study the cellular localization and function of tetraspanin molecules, which have been postulated to modulate integrin activity. We found that CD9 and **CD81** are highly expressed by keratinocytes clearly delineating filopodia at lateral and apical surfaces. CD63 and CD151 are largely expressed in the intracellular compartment, although some membrane expression is observed. We found accumulation of CD9, **CD81**, and CD151 together with alpha3 and betal integrins at intercellular junctions. In low calcium medium, this intercellular space is crossed by a zipper of filopodia enriched in alpha3beta1 and tetraspanin proteins. Interestingly, the expression of CD9, **CD81**, and betal and alpha3 integrins was detected in the footprints and rippings of motile keratinocytes, suggesting their role in both adhesion to extracellular matrix and keratinocyte motility. betal integrins were only partially activated in the rips, whereas cytoskeleton-linking proteins such as talin were completely absent. On the other hand,

antitetranspanin antibodies did not stain focal adhesions, which contain talin. The involvement of tetraspanins in keratinocyte motility was assessed in a wound healing migration assay. Inhibition of cell migration was observed with antibodies to CD9, **CD81**, betal, and alpha3, and, to a lesser extent, to CD151. Together these results indicate that tetraspanin-integrin complexes might be involved in transient adhesion and integrin recycling during keratinocyte migration, as well as in intercellular recognition.

5/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10471384 20117181 PMID: 10653456
Hepatitis C--virology and future antiviral targets.
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Department of Internal Medicine, Saint Louis University School of Medicine, Missouri 63104, USA.

American journal of medicine (UNITED STATES) Dec 27 1999, 107 (6B)
p45S-48S, ISSN 0002-9343 Journal Code: 3JU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The hepatitis C virus is a single-stranded RNA virus with a genome approximately 9,000 nucleotides in length. The genome consists of a single, large open reading frame (ORF) and 5' and 3' untranslated regions. The highly conserved 5' untranslated region is 341 nucleotides in length with a complex secondary structure and may function as an internal ribosomal entry site (IRES). The 3' untranslated region is approximately 500 nucleotides in length and contains a hypervariable region, followed by a poly(U) sequence and a highly conserved 98-nucleotide element with a stable secondary structure. The ORF codes form a single polyprotein that is processed into as many as 10 polypeptides, including a capsid protein (core), two envelope proteins (E1 and E2), and nonstructural proteins (NS2, NS3, NS4, and NS5). Potentially suitable antiviral targets include the IRES, protease, helicase, and RNA polymerase. In vitro studies show that antisense oligonucleotides can inhibit the production of structural HCV proteins and may be therapeutically useful if the problems of stability and delivery can be solved. The binding of HCV envelope proteins to **CD81**, a potential receptor for viral entry into hepatocytes, has recently been described and also raises the possibility of agents to block the binding to **CD81** or the entry of the virus into cells.

5/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10337387 99228216 PMID: 10213228
Antitumor activity of sequential treatment with topotecan and anti-epidermal growth factor receptor monoclonal antibody C225.

Ciardiello F; Bianco R; Damiano V; De Lorenzo S; Pepe S; De Placido S; Fan Z; Mendelsohn J; Bianco AR; Tortora G

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Clinical cancer research (UNITED STATES) Apr 1999, 5 (4) p909-16,
ISSN 1078-0432 Journal Code: C2H

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Epidermal growth factor (EGF)-related proteins such as transforming growth factor alpha (TGF-alpha) control cancer cell growth through autocrine and paracrine pathways. Overexpression of TGF-alpha and/or its receptor (EGFR) has been associated with a more aggressive disease and a

poor prognosis. The blockade of EGFR activation has been proposed as a target for anticancer therapy. Monoclonal antibody (MAb) C225 is an anti-EGFR humanized chimeric mouse MAb that is presently in Phase II clinical trials in cancer patients. Previous studies have suggested the potentiation of the antitumor activity of certain cytotoxic drugs, such as cisplatin and doxorubicin, in human cancer cell lines by treatment with anti-EGFR antibodies. We have evaluated in human ovarian, breast, and colon cancer cell lines, which express functional EGFR, the antiproliferative activity of MAb C225 in combination with topotecan, a cytotoxic drug that specifically inhibits topoisomerase I and that has shown antitumor activity in these malignancies. A dose-dependent supraadditive increase of growth inhibition in vitro was observed when cancer cells were treated with topotecan and MAb C225 in a sequential schedule. In this respect, the cooperativity quotient, defined as the ratio between the actual growth inhibition obtained by treatment with topotecan followed by MAb C225 and the sum of the growth inhibition achieved by each agent, ranged from 1.2 to 3, depending on drug concentration and cancer cell line. Treatment with MAb C225 also markedly enhanced apoptotic cell death induced by topotecan. For example, in GEO colon cancer cells, 5 nM topotecan, followed by 0.5 microg/ml MAb C225, induced apoptosis in 45% cells as compared with untreated cells (6%) or to 5 nM topotecan-treated cells (22%). Treatment of mice bearing established human GEO colon cancer xenografts with topotecan or with MAb C225 determined a transient inhibition of tumor growth because GEO tumors resumed the growth rate of untreated tumors at the end of the treatment period. In contrast, an almost complete tumor regression was observed in all mice treated with the two agents in combination. This determined a prolonged life span of the mice that was significantly different as compared with controls ($P < 0.001$), to MAb C225-treated group ($P < 0.001$), or to the topotecan-treated group ($P < 0.001$). All mice of the topotecan plus MAb C225 group were the only animals alive 14 weeks after tumor cell injection. Furthermore, 20% of mice in this group were still alive after 19 weeks. The combined treatment with MAb C225 and topotecan was well tolerated by mice with no signs of acute or delayed toxicity. These results provide a rationale for the evaluation of the anticancer activity of the combination of topoisomerase I inhibitors and anti-EGFR blocking MAbs in clinical trials.

5/3,AB/32 (Item 32 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10300851 98189267 PMID: 9514697

Functional analysis of four tetraspans, CD9, CD53, CD81, and CD82, suggests a common role in costimulation, cell adhesion, and migration: only CD9 upregulates HB-EGF activity.

Lagaudriere-Gesbert C; Le Naour F; Lebel-Binay S; Billard M; Lemichez E; Boquet P; Boucheix C; Conjeaud H; Rubinstein E

INSERM U283, Hopital Cochin, Paris, France.

Cellular immunology (UNITED STATES) Dec 15 1997, 182 (2) p105-12,
ISSN 0008-8749 Journal Code: CQ9

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Molecules of the tetraspan superfamily are engaged in multimolecular complexes containing other proteins such as beta 1 integrins and MHC antigens. Although their functions are not clear, they have been suggested to play a role in cell adhesion and migration, signal transduction, and costimulation. We have in this paper directly compared the functional properties of four tetraspans, CD9, CD53, CD81, and CD82. mAbs to any of these molecules were able to deliver a costimulatory signal for CD3-mediated activation of the T cell line Jurkat. CD82 mAbs were the most efficient in triggering this effect. Moreover, engagement of CD9, CD81, and CD82 induced the homotypic aggregation of the

megakaryocytic cell line HEL, and inhibited the migration of this cell line. Similar results were obtained with the preB cell line NALM-6 using the CD9 and **CD81** mAbs. The **CD81** mAb 5A6 produced the strongest effects. Therefore, the tetraspans are recognized by mAbs which produce similar effects on the same cell lines. This is consistent with the tetraspans being included in large molecular complexes and possibly forming a tetraspan network (the tetraspan web). We also demonstrate that the tetraspans are likely to keep specific functional properties inside this network. Indeed, we have demonstrated that the human CD9 is able, like the monkey molecule, to upregulate the activity of the transmembrane precursor of heparin-binding EGF as a receptor for the diphtheria toxin when cotransfected in murine LM cells. Neither **CD81**, nor CD82 had such activity. By using chimeric CD9/**CD81** molecules we demonstrate that this activity requires the second half of CD9, which contains the large extracellular loop, the fourth transmembrane region, and the last short cytoplasmic domain.

5/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10254858 99389749 PMID: 10459022
Role of transmembrane 4 superfamily (TM4SF) proteins CD9 and **CD81** in muscle cell fusion and myotube maintenance.
Tachibana I; Hemler ME
Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts 02115, USA.

Journal of cell biology (UNITED STATES) Aug 23 1999, 146 (4)
p893-904, ISSN 0021-9525 Journal Code: HMV
Contract/Grant No.: GM38903, GM, NIGMS
Languages: ENGLISH

Document type: Journal Article
Record type: Completed

The role of transmembrane 4 superfamily (TM4SF) proteins during muscle cell fusion has not been investigated previously. Here we show that the appearance of TM4SF protein, CD9, and the formation of CD9-beta1 integrin complexes were both regulated in coordination with murine C2C12 myoblast cell differentiation. Also, anti-CD9 and anti-**CD81** monoclonal antibodies substantially inhibited and delayed conversion of C2C12 cells to elongated myotubes, without affecting muscle-specific protein expression. Studies of the human myoblast-derived RD sarcoma cell line further demonstrated that TM4SF proteins have a role during muscle cell fusion. Ectopic expression of CD9 caused a four- to eightfold increase in RD cell syncytia formation, whereas anti-CD9 and anti-**CD81** antibodies markedly delayed RD syncytia formation. Finally, anti-CD9 and anti-**CD81** monoclonal antibodies triggered apoptotic degeneration of C2C12 cell myotubes after they were formed. In summary, TM4SF proteins such as CD9 and **CD81** appear to promote muscle cell fusion and support myotube maintenance.

5/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10225402 99329140 PMID: 10400713
Characterization of hepatitis C virus E2 glycoprotein interaction with a putative cellular receptor, **CD81**.

Flint M; Maidens C; Loomis-Price LD; Shotton C; Dubuisson J; Monk P; Higginbottom A; Levy S; McKeating JA
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Journal of virology (UNITED STATES) Aug 1999, 73 (8) p6235-44,
ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: CA34233, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

A truncated soluble form of the hepatitis C virus E2 glycoprotein, E2661, binds specifically to the surface of cells expressing human **CD81** (hCD81) but not other members of the tetraspanin family (CD9, CD63, and CD151). No differences were noted between the level of E2661 binding to hCD81 expressed on the surface of rat RBL or KM3 cells compared to Daudi and Molt-4 cells, suggesting that additional human-cell-specific factors are not required for the primary interaction of E2 with the cell surface. E2 did not interact with African green monkey (AGM) **CD81** on the surface of COS cells, which differs from the hCD81 sequence at four residues within the second extracellular region (EC2) (amino acids [aa] 163, 186, 188, and 196), suggesting that one or more of these residues defines the site of interaction with E2. Various recombinant forms of **CD81** EC2 show differences in the ability to bind E2, suggesting that **CD81** conformation is important for E2 recognition. Regions of E2 involved in the **CD81** interaction were analyzed, and our data suggest that the binding site is of a conformational nature involving aa 480 to 493 and 544 to 551 within the E2 glycoprotein. Finally, we demonstrate that ligation of **CD81** by E2661 induced aggregation of lymphoid cells and inhibited B-cell proliferation, demonstrating that E2 interaction with **CD81** can modulate cell function.

5/3,AB/35 (Item 35 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10099581 99131987 PMID: 9931299

Transmembrane 4 superfamily protein CD151 (PETA-3) associates with beta 1 and alpha IIb beta 3 integrins in haemopoietic cell lines and modulates cell-cell adhesion.

Fitter S; Sincock PM; Jolliffe CN; Ashman LK

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Biochemical journal (ENGLAND) Feb 15 1999, 338 (Pt 1) p61-70, ISSN 0264-6021 Journal Code: 9YO

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD151 (PETA-3/SFA-1) is a member of the transmembrane 4 superfamily (TM4SF) of cell-surface proteins and is expressed abundantly both on the cell surface and in intracellular membranes by the haemopoietic cell lines M07e, HEL and K562. In the presence of mild detergent (CHAPS), CD151 co-immunoprecipitated with integrin alpha 4 beta 1, alpha 5 beta 1, alpha 6 beta 1 and alpha IIb beta 3. The association of CD151 with alpha 4 beta 1 and alpha 5 beta 1 seemed to be constitutive, as it was not modified by treatment of M07e cells with cytokines that regulate integrin function by 'inside-out' signalling. CD151 also associated with other tetraspans in an apparently cell-type-specific fashion, as defined by its co-precipitation with CD9, CD63 and **CD81** from M07e cells, but not from K562 cells, which express similar levels of these proteins. F(ab')2 fragments of monoclonal antibodies (mAbs) against CD151 caused homotypic adhesion of HEL and K562 cells that was dependent on energy and cytoskeletal integrity and was augmented in the presence of RGDS peptides. The adhesion was not blocked by function-inhibiting mAbs against beta 1 or beta 3 integrins, suggesting that cell-cell adhesion was not mediated by the binding of integrin to a cell-associated ligand. Furthermore, mAb CD151 did not affect adhesion of the cells to fibronectin, laminin, collagen or fibrinogen, which are ligands for alpha 4 beta 1, alpha 5 beta 1, alpha 6 beta 1 and alpha IIb beta 3 integrins. Taken together, these results indicate that the ligation of CD151 does not induce the up-regulation of integrin avidity, but might act as a component of integrin signalling complexes.

5/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09973870 99077164 PMID: 9862348

Gamma-glutamyl transpeptidase, an ecto-enzyme regulator of intracellular redox potential, is a component of TM4 signal transduction complexes.

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European journal of immunology (GERMANY) Dec 1998, 28 (12) p4123-9,
ISSN 0014-2980 Journal Code: EN5

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD21 (C3dg/EBV receptor) is physically associated on B cells with a complex of proteins that includes CD19 and the widely distributed tetraspan 4 (TM4) family protein **CD81** as well as other TM4 proteins (CD53, CD37 and CD82). Monoclonal antibodies (mAb) were generated that blocked homotypic adhesion induced by CD21 ligands in the human B cell line Balm-1. One **inhibitory** mAb (3A8) was found to recognize the ecto-enzyme gamma-glutamyl transpeptidase (GGT), a membrane protein involved in recycling extracellular glutathione and regulating intracellular redox potential. Molecular associations between GGT and TM4 proteins **CD81**, CD53 and CD82, in addition to CD21 and CD19, were detected by co-precipitation and co-capping analysis. GGT is expressed on several B and T cell lines independently of CD21 expression. These results demonstrate that GGT is a component of widely distributed TM4 complexes, and that on B cells the GGT-containing TM4 complexes also contain CD19 and CD21.

5/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09940078 99030705 PMID: 9812906

Tetraspanin CD9 is associated with very late-acting integrins in human vascular smooth muscle cells and modulates collagen matrix reorganization.

Scherberich A; Moog S; Haan-Archipoff G; Azorsa DO; Lanza F; Beretz A

Laboratoire de Pharmacologie et Physiologie Cellulaires, Faculte de Pharmacie, Illkirch France.

Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) Nov 1998, 18 (11) p1691-7, ISSN 1079-5642 Journal Code: B89

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD9, a member of the tetraspanin family, and very late-acting (VLA) integrins are known to associate and form functional units on the surface of several cell types. We studied the changes in expression of CD9 and beta1-integrins (CD29, VLA) in human vascular smooth muscle cells (VSMCs) under *in vitro* culture conditions mimicking proliferative vascular diseases. We also investigated possible interactions between CD9 and VLA integrins in VSMCs. We found that CD9 is highly expressed in VSMCs and is subject to modulation, depending on the proliferative/contractile state of the cells. In the contractile phenotype, the levels of CD9, **CD81**, another tetraspanin, and CD29 are approximately 50% of those found in the proliferative phenotype. Coimmunoprecipitation experiments showed physical association between CD9 and CD29. CD9 was mainly associated with alpha2 and alpha3-integrins (CD49b and c) and also with alpha5-integrin to a weaker extent. Functionally, the addition of anti-CD9 monoclonal antibodies (MoAbs) doubled the extent of collagen gel contraction mediated by VSMCs, a model for the reorganization of the extracellular collagen matrix occurring in the vessel wall. Anti-CD29 MoAbs **inhibited** gel contraction, but anti-CD9 MoAbs counteracted this **inhibitory** effect of anti-CD29

MoAbs. Transfection of human CD9 into Chinese hamster ovary cells more than doubled the extent of Chinese hamster ovary cell-mediated collagen gel contraction (130% stimulation), confirming a role for CD9 in extracellular matrix reorganization. Thus, CD9 seems to be involved in the modulation of VLA integrin-mediated collagen matrix reorganization by VSMCs. These findings suggest that high CD9 expression is associated with a proliferative state of VSMCs. The role of CD9 could be to modulate the function of VLA integrins on the surface of VSMCs.

5/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

09928308 99011351 PMID: 9794763
Binding of hepatitis C virus to **CD81**.
Pileri P; Uematsu Y; Campagnoli S; Galli G; Falugi F; Petracca R; Weiner AJ; Houghton M; Rosa D; Grandi G; Abrignani S
IRIS, Chiron, Siena 53100, Italy.
Science (UNITED STATES) Oct 30 1998, 282 (5390) p938-41, ISSN 0036-8075 Journal Code: UJ7

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Chronic hepatitis C virus (HCV) infection occurs in about 3 percent of the world's population and is a major cause of liver disease. HCV infection is also associated with cryoglobulinemia, a B lymphocyte proliferative disorder. Virus tropism is controversial, and the mechanisms of cell entry remain unknown. The HCV envelope protein E2 binds human **CD81**, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes. Binding of E2 was mapped to the major extracellular loop of **CD81**. Recombinant molecules containing this loop bound HCV and antibodies that neutralize HCV infection in vivo inhibited virus binding to **CD81** in vitro.

5/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

09755633 98234412 PMID: 9566977
Regulation of endothelial cell motility by complexes of tetraspan molecules **CD81/TAPA-1** and CD151/PETA-3 with alpha3 beta1 integrin localized at endothelial lateral junctions.

Yanez-Mo M; Alfranca A; Cabanas C; Marazuela M; Tejedor R; Ursu MA; Ashman LK; de Landazuri MO; Sanchez-Madrid F

Servicio de Inmunologia, Hospital de la Princesa, Universidad Autonoma de Madrid.

Journal of cell biology (UNITED STATES) May 4 1998, 141 (3) p791-804
, ISSN 0021-9525 Journal Code: HMV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Cell-to-cell junction structures play a key role in cell growth rate control and cell polarization. In endothelial cells (EC), these structures are also involved in regulation of vascular permeability and leukocyte extravasation. To identify novel components in EC intercellular junctions, mAbs against these cells were produced and selected using a morphological screening by immunofluorescence microscopy. Two novel mAbs, LIA1/1 and VJ1/16, specifically recognized a 25-kD protein that was selectively localized at cell-cell junctions of EC, both in the primary formation of cell monolayers and when EC reorganized in the process of wound healing. This antigen corresponded to the recently cloned platelet-endothelial tetraspan antigen CD151/PETA-3 (platelet-endothelial tetraspan antigen-3), and was consistently detected at EC cell-cell contact sites. In addition to CD151/PETA-3, two other members of the tetraspan superfamily, CD9 and

CD81/ TAPA-1 (target of antiproliferative antibody-1), localized at endothelial cell-to-cell junctions. Biochemical analysis demonstrated molecular associations among tetraspan molecules themselves and those of CD151/ PETA-3 and CD9 with alpha3 beta1 integrin. Interestingly, mAbs directed to both CD151/PETA-3 and **CD81/TAPA-1** as well as mAb specific for alpha3 integrin, were able to inhibit the migration of ECs in the process of wound healing. The engagement of CD151/PETA-3 and **CD81/TAPA-1** inhibited the movement of individual ECs, as determined by quantitative time-lapse video microscopy studies. Furthermore, mAbs against the CD151/PETA-3 molecule diminished the rate of EC invasion into collagen gels. In addition, these mAbs were able to increase the adhesion of EC to extracellular matrix proteins. Together these results indicate that **CD81/TAPA-1** and CD151/PETA-3 tetraspan molecules are components of the endothelial lateral junctions implicated in the regulation of cell motility, either directly or by modulation of the function of the associated integrin heterodimers.

5/3,AB/40 (Item 40 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09559227 97389378 PMID: 9265505
Synergy between anti-CD40 MAb and Epstein-Barr virus in activation and transformation of human B lymphocytes.
Tsuchiyama L; Kieran J; Boyle P; Wetzel GD
Preclinical Biology Research, Bayer Corp., Berkeley, CA 94701, USA.
Human antibodies (UNITED STATES) 1997, 8 (1) p43-7, ISSN 1093-2607

Journal Code: CU3

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

For human B lymphocytes, Epstein-Barr virus (EBV) is a polyclonal activator, inducing both proliferation and Ig secretion. It is also a transforming virus capable of generating immortalized B cell lines. These early and late functions of EBV are not apparently connected. The receptor for EBV, CD21, also serves as a receptor for some complement components and is called CR2. This molecule associates with CD19 and **TAPA-1** on the surface of B cells. This complex is involved in signaling B cells and participates in many responses. We have observed that simultaneous ligation of CD40 and the CD21 complex, by exposure to anti-CD40 MAbs and EBV, enhances both the short-term proliferation as well as the long-term transformation rate of human B lymphocytes. B cell proliferation shows synergy between anti-CD40 MAb and EBV. CD19 also appears to be involved in the synergistic activation of B cells through CD40 and CD21, since ligation of CD19 with anti-CD19 MAbs, either prior to or concomitant with exposure to anti-CD40 and EBV, markedly inhibits both proliferation and subsequent B cell transformation. These observations do not elucidate the mechanisms of B cell transformation employed by EBV but they do suggest a relationship between early proliferation and later transformation induced by the virus. Anti-CD40 enhances both these effects and anti-CD19 is capable of inhibiting both.

5/3,AB/41 (Item 41 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09447079 98001686 PMID: 9341151
Purification and characterization of the human SR 31747A-binding protein. A nuclear membrane protein related to yeast sterol isomerase.
Jbilo O; Vidal H; Paul R; De Nys N; Bensaid M; Silve S; Carayon P; Davi D; Galiegue S; Bourrie B; Guillemot JC; Ferrara P; Loison G; Maffrand JP; Le Fur G; Casellas P
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Journal of biological chemistry (UNITED STATES) Oct 24 1997, 272 (43)
p27107-15, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

SR 31747A, defined as a sigma ligand, is a novel immunosuppressive agent that blocks proliferation of human and mouse lymphocytes. Using a radiolabeled chemical probe, we here purified a **target** of SR 31747A and called it SR 31747A-binding protein (SR-BP). Purified SR-BP retained its binding properties and migrated on SDS-polyacrylamide gel as a Mr 28,000 protein. Cloning of the cDNA encoding human SR-BP shows an open reading frame for a 223-amino acid protein, which is homologous to the recently cloned sigma 1 receptor. Interestingly, the deduced amino acid sequence was found to be related to fungal C8-C7 sterol isomerase, encoded by the ERG2 gene. The ERG2 gene product has been identified recently as the molecular **target** of SR 31747A that mediates **antiproliferative** effects of the drug in yeast. Northern blot analysis of SR-BP gene expression revealed a single transcript of 2 kilobases which was widely expressed among organs, with the highest abundance in liver and the lowest abundance in brain. Subcellular localization analysis in various cells, using a specific monoclonal **antibody** raised against SR-BP, demonstrated that this protein was associated with the nuclear envelope. When studying the binding of SR 31747A on membranes from yeast expressing SR-BP, we found a pharmacological profile of sigma 1 receptors; binding was displaced by (+)-pentazocine, haloperidol, and (+)-SKF 10,047, with (+)-SKF 10,047 being a more potent competitor than (-)-SKF 10,047. Scatchard plot analysis revealed Kd values of 7.1 nM and 0.15 nM for (+)-pentazocine and SR 31747A, respectively, indicating an affinity of SR-BP 50-fold higher for SR 31747A than for pentazocine. Additionally, we showed that pentazocine, a competitive **inhibitor** of SR 31747A binding, also prevents the immunosuppressive effect of SR 31747A. Taken together, these findings strongly suggest that SR-BP represents the molecular **target** for SR 31747A in mammalian tissues, which could be critical for T cell proliferation.

5/3,AB/42 (Item 42 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09438242 98028160 PMID: 9362067
Integrin alpha 6A beta 1 induces **CD81**-dependent cell motility without engaging the extracellular matrix migration substrate.
Domanico SZ; Pelletier AJ; Havran WL; Quaranta V
Department of Cell Biology, Scripps Research Institute, La Jolla, California 92037, USA.
Molecular biology of the cell (UNITED STATES) Nov 1997, 8 (11)
p2253-65, ISSN 1059-1524 Journal Code: BAU
Contract/Grant No.: CA-47858, CA, NCI; DE-10063, DE, NIDCR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

It is well established that integrins and extracellular matrix (ECM) play key roles in cell migration, but the underlying mechanisms are poorly defined. We describe a novel mechanism whereby the integrin alpha 6 beta 1, a laminin receptor, can affect cell motility and induce migration onto ECM substrates with which it is not engaged. By using DNA-mediated gene transfer, we expressed the human integrin subunit alpha 6A in murine embryonic stem (ES) cells. ES cells expressing alpha 6A (ES6A) at the surface dimerized with endogenous beta 1, extended numerous filopodia and lamellipodia, and were intensely migratory in haptotactic assays on laminin (LN)-1. Transfected alpha 6A was responsible for these effects, because cells transfected with control vector or alpha 6B, a cytoplasmic domain alpha 6 isoform, displayed compact morphology and no migration, like

wild-type ES cells. The ES6A migratory phenotype persisted on fibronectin (Fn) and Ln-5. Adhesion **inhibition** assays indicated that alpha 6 beta 1 did not contribute detectably to adhesion to these substrates in ES cells. However, anti-alpha 6 antibodies completely blocked migration of ES6A cells on Fn or Ln-5. Control experiments with monensin and anti-ECM antibodies indicated that this **inhibition** could not be explained by deposition of an alpha 6 beta 1 ligand (e.g., Ln-1) by ES cells. Cross-linking with secondary antibody overcame the **inhibitory** effect of anti-alpha 6 antibodies, restoring migration or filopodia extension on Fn and Ln-5. Thus, to induce migration in ES cells, alpha 6A beta 1 did not have to engage with an ECM ligand but likely participated in molecular interactions sensitive to anti-alpha 6 beta 1 antibody and mimicked by cross-linking. Antibodies to the tetraspanin **CD81 inhibited** alpha 6A beta 1-induced migration but had no effect on ES cell adhesion. It is known that **CD81** is physically associated with alpha 6 beta 1, therefore our results suggest a mechanism by which interactions between alpha 6A beta 1 and **CD81** may up-regulate cell motility, affecting migration mediated by other integrins.

5/3,AB/43 (Item 43 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09423142 97477414 PMID: 9334370
Negative regulation of Fc epsilon RI-mediated degranulation by **CD81**

Fleming TJ; Donnadieu E; Song CH; Laethem FV; Galli SJ; Kinet JP
Department of Pathology, Beth Israel Deaconess Medical Center, Boston,
Massachusetts 02215, USA.

Journal of experimental medicine (UNITED STATES) Oct 20 1997, 186 (8)
p1307-14, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: AI/CA-23990, AI, NIAID; CA/AI-72074, CA, NCI;
GM-53950, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Signaling through the high affinity receptor for immunoglobulin E (Fc epsilon RI) results in the coordinate activation of tyrosine kinases before calcium mobilization. Receptors capable of interfering with the signaling of antigen receptors, such as Fc epsilon RI, recruit tyrosine and inositol phosphatases that results in diminished calcium mobilization. Here, we show that antibodies recognizing **CD81 inhibit** Fc epsilon RI-mediated mast cell degranulation but, surprisingly, without affecting aggregation-dependent tyrosine phosphorylation, calcium mobilization, or leukotriene synthesis. Furthermore, **CD81** antibodies also **inhibit** mast cell degranulation *in vivo* as measured by reduced passive cutaneous anaphylaxis responses. These results reveal an unsuspected calcium-independent pathway of antigen receptor regulation, which is accessible to engagement by membrane proteins and on which novel therapeutic approaches to allergic diseases could be based.

5/3,AB/44 (Item 44 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09409511 98010045 PMID: 9349332
Presence of somatostatin in normal human epidermis.
Gaudillere A; Misery L; Bernard C; Souchier C; Claudy A; Schmitt D
INSERM U346, E. Herriot Hospital, Lyon, France.

British journal of dermatology (ENGLAND) Sep 1997, 137 (3) p376-80,
ISSN 0007-0963 Journal Code: AWO

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Somatostatin (SOM) is a ubiquitous peptide which is responsible for the inhibition of numerous biological functions. SOM is described as an antiproliferative molecule and an inhibitor of exocrine or endocrine secretion from a variety of tissues, including pancreas, gastrointestinal tract, central and peripheral nervous system. Mediation of SOM effects can be indirect or direct, respectively, through other molecules or receptors on target cells. We have searched for the presence of SOM in the epidermis using immunofluorescence, confocal laser scanning microscopy, radioimmunoassay, and chromatography. Immunofluorescence and confocal laser scanning microscopy studies were performed using rabbit antiserum anti-SOM and mouse monoclonal antibody directed to CD1a Langerhans cell (LC) marker disclosed with fluorescein or tetramethylrhodamine isothiocyanate conjugates. SOM was extracted from whole skin or epidermal cell suspension or LC-enriched suspensions and analysed by radioimmunoassay. We used an antiserum which was reactive for the 6-11 portion of native SOM. Chromatographic columns were performed on extracts from whole skin. The epidermis was SOM immunoreactive. LC were immunoreactive for SOM and the staining was membranous. SOM was extracted from the whole skin at about 0.13 +/- 0.02 fmol/mg of tissue (mean +/- SEM). The SOM concentration in epidermal cell suspensions was 1.5 +/- 0.9 fmol/10⁶ cells. Data obtained with LC-enriched suspensions showed large variations between donors. Extracts from skin showed one peak with an elution profile like that of 14 amino acid SOM. This study demonstrates that 14 amino acid SOM is expressed in normal human epidermis.

5/3,AB/45 (Item 45 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09394615 97160557 PMID: 9006891

A novel link between integrins, transmembrane-4 superfamily proteins (CD63 and **CD81**), and phosphatidylinositol 4-kinase.

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Dana-Farber Cancer Institute, Harvard Medical School, Boston,
Massachusetts 02115, USA.

Journal of biological chemistry (UNITED STATES) Jan 31 1997, 272 (5)
p2595-8, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: GM38903, GM, NIGMS; GM54387, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Enzymatic and immunochemical assays show a phosphatidylinositol 4-kinase in novel and specific complexes with proteins (CD63 and **CD81**) of the transmembrane 4 superfamily (TM4SF) and an integrin (alpha3beta1). The size (55 kDa) and other properties of the phosphatidylinositol 4-kinase (PI 4-K) (stimulated by nonionic detergent, inhibited by adenosine, inhibited by monoclonal antibody 4CG5) are consistent with PI 4-K type II. Not only was PI 4-K associated with alpha3beta1-CD63 complexes in alpha3-transfected K562 cells, but also it could be co-purified from CD63 in untransfected K562 cells lacking alpha3beta1. Thus, TM4SF proteins may link PI 4-K activity to the alpha3beta1 integrin. The alpha5beta1 integrin, which does not associate with TM4SF proteins, was not associated with PI 4-K. Notably, alpha3beta1-CD63-**CD81**-PI 4-K complexes are located in focal complexes at the cell periphery rather than in focal adhesions. The novel linkage between integrins, transmembrane 4 proteins, and phosphoinositide signaling at the cell periphery may play a key role in cell motility and provides a signaling pathway distinct from conventional integrin signaling through focal adhesion kinase.

5/3,AB/46 (Item 46 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09327681 97307622 PMID: 9164964

Tyrosine kinase-dependent regulation of L-selectin expression through the Leu-13 signal transduction molecule: evidence for a protein kinase C-independent mechanism of L-selectin shedding.

Frey M; Appenheimer MM; Evans SS

Department of Molecular Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

Journal of immunology (UNITED STATES) Jun 1 1997, 158 (11) p5424-34, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: P30 CA16056-21, CA, NCI; RR08926, RR, NCRR

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The L-selectin adhesion molecule mediates lymphocyte extravasation in peripheral lymph nodes, and has also been implicated in directing leukocyte recruitment to inflammatory tissues and metastasis of lymphoid malignancies. In this study, we demonstrate a novel level of regulation of L-selectin expression that involves the 16-kDa Leu-13 signal transduction molecule. Leu-13 is a member of a multimeric cell surface complex in lymphocytes that includes TAPA-1 (target of antiproliferative Ab-1, CD81) as well as lineage-specific proteins. In the present study, mAb-induced ligation of Leu-13 was shown to rapidly down-regulate L-selectin surface density on normal and malignant human lymphocytes, and to markedly inhibit L-selectin-mediated adhesion of lymphocytes to soluble carbohydrate ligands (i.e., PPME, phosphomonoester core polysaccharide) and to lymph node high endothelial venules. Through the use of genistein and staurosporine, potent inhibitors of tyrosine kinases (TK) and protein kinase C (PKC), respectively, Leu-13-induced L-selectin down-modulation was demonstrated to involve a TK-dependent, PKC-independent pathway, and was attributed to increased L-selectin shedding from surface membranes. Notably, direct L-selectin ligation, modeling cross-linking interactions with endothelial cell ligands, similarly down-regulates L-selectin surface expression through a TK-dependent, PKC-independent mechanism. In sharp contrast, PMA and anti-CD3 mAb down-regulate L-selectin via a staurosporine-sensitive, genistein-resistant pathway that is closely linked to lymphocyte proliferation. Taken together, these results demonstrate a novel role for Leu-13- and L-selectin-induced TK activity in control of L-selectin expression, thus providing insight into the complex molecular mechanisms that potentially regulate L-selectin-dependent lymphocyte homing in vivo.

5/3,AB/47 (Item 47 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09312604 97300512 PMID: 9155533

In vitro synergy of paclitaxel (Taxol) and vinorelbine (navelbine) against human melanoma cell lines.

Photiou A; Shah P; Leong LK; Moss J; Retsas S

Catherine Griffiths Cancer Research Laboratory, Department of Medical Oncology, Charing Cross Hospital, London, U.K.

European journal of cancer (ENGLAND) Mar 1997, 33 (3) p463-70, ISSN 0959-8049 Journal Code: ARV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Paclitaxel (PTXL) (Taxol), a taxane, and vinorelbine (VRB), a semisynthetic vinca alkaloid drug, have tubulin as their common intracellular target, but inhibit growth by binding to different sites. We evaluated in vitro the antiproliferative activity of these two drugs as single agents and in combination, against two human melanoma cell lines, G361 and StM11a. The SRB (sulphorhodamine B) assay was used to determine growth inhibition. Possible drug-drug interaction at the cellular level was assessed by constructing Isoboles

(Isobologram analysis) and applying the concept of an 'envelope of additivity'. Both agents were active in the nanomolar range at clinically achievable concentrations. The mean IC₅₀ for G361 was 46.6 nM (PTXL) and 19.9 nM (VRB) after a 1 h drug exposure. Mean IC₅₀ (1 h) for StM111a was 9.7 nM (PTXL) and 26.9 nM (VRB). Isobole analysis at the isoeffect levels of 25%, 50% and 75% indicated that drug interaction was predominantly synergistic (supra-additive) when paclitaxel and VRB were added concurrently for 1 h to cultures of StM111a or G361. In some experiments, this synergy was observed with particularly low concentrations of paclitaxel (3 nM) and VRB (0.01 nM). A new point was located within the envelope of additivity or in the subadditive (antagonism) region of the isobole. An overall synergy was also found if the data were analysed by the median effect analysis. The effect of these agents on the cytoskeleton and ultrastructure were studied with immunofluorescence and electron microscopy, respectively. These results confirm the *in vitro* inhibitory activity of paclitaxel and VRB against malignant melanoma, but more importantly the two drugs appear to act synergistically at relatively low concentrations.

5/3,AB/48 (Item 48 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09278738 97230155 PMID: 9075733

A monoclonal antibody against rat calcitonin inhibits the growth of a rat medullary thyroid carcinoma cell line *in vitro*.

Zhang R; DeGroot LJ
Department of Medicine, University of Chicago, Illinois 60637, USA.
Endocrinology (UNITED STATES) Apr 1997, 138 (4) p1697-703, ISSN 0013-7227 Journal Code: EGZ

Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Medullary thyroid carcinoma (MTC) cells synthesize large amounts of calcitonin (CT), which serves clinically as a useful tumor marker. To examine the possibility of CT serving as a target in immunotherapy for MTC, we raised and characterized more than 40 monoclonal antibodies (mAbs) against rat CT (rCT). The affinity constants for the mAbs were between $2.8 \times 10(9)$ and $1.8 \times 10(11)$ M(-1). Some mAbs react preferentially with solid phase rat CT, but not with liquid phase ¹²⁵I-labeled rCT. Thirty-nine mAbs cross-react with human CT. We evaluated the antitumor effect of the mAbs *in vitro* by analysis of [³H]thymidine incorporation into the rat MTC cell line CRL-1607. Some antibodies show an antiproliferative effect, but most are inactive. One mAb (2E5G5, IgG2b), which preferentially reacts with solid phase rCT, but not with liquid phase ¹²⁵I-labeled rCT, exerts an antiproliferative activity on CRL-1607. At $6.25 \times 10(-7)$ M, 2E5G5 killed all of the tumor cells independently of complement in a cytotoxicity assay. We explored the cytotoxic mechanisms by assays for cell cycle arrest and DNA fragmentation. The antitumor effect was manifested by apoptosis and cell cycle arrest. Hence, a secreted peptide may serve as a target in tumor immunotherapy. Therapeutically antibodies may exert antitumor activity by a variety of mechanisms. The antitumor effect of this mAb in a rat animal tumor model is being tested.

5/3,AB/49 (Item 49 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09269258 97211760 PMID: 9058727

CD30 ligand is frequently expressed in human hematopoietic malignancies of myeloid and lymphoid origin.

Gattei V; Degan M; Gloghini A; De Iuliis A; Impronta S; Rossi FM; Aldinucci D; Perin V; Serraino D; Babare R; Zagonel V; Gruss HJ; Carbone A;

Pinto A

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Aviano, Italy.

Blood (UNITED STATES) Mar 15 1997, 89 (6) p2048-59, ISSN 0006-4971

Journal Code: A8G

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD30 ligand (CD30L) is a type-II membrane glycoprotein capable of transducing signals leading to either cell death or proliferation through its specific counterstructure CD30. Although several lines of evidence indicate that CD30L plays a key role as a paracrine- or autocrine-acting surface molecule in the deregulated cytokine cascade of Hodgkin's disease, little is known regarding its distribution and biologic significance in other human hematopoietic malignancies. By analyzing tumor cells from 181 patients with RNA studies and immunostaining by the anti-CD30L monoclonal antibody M80, we were able to show that human hematopoietic malignancies of different lineage and maturation stage display a frequent and broad expression of the ligand. CD30L mRNA and surface protein were detected in 60% of acute myeloid leukemias (AMLS), 54% of B-lineage acute lymphoblastic leukemias (ALLs), and in a consistent fraction (68%) of B-cell lymphoproliferative disorders. In this latter group, hairy cell leukemia and high-grade B-cell non-Hodgkin's lymphoma (B-NHL) expressed a higher surface density of CD30L as compared with B-cell chronic lymphocytic leukemia and low-grade B-NHL. Purified plasmacells from a fraction of multiple myeloma patients also displayed CD30L mRNA and protein. A more restricted expression of CD30L was found in T-cell tumors that was mainly confined to neoplasms with an activated peripheral T-cell phenotype, such as T-cell prolymphocytic leukemia, peripheral T-NHL, and adult T-cell leukemia/lymphoma. In contrast, none of the T-lineage ALLs analyzed expressed the ligand. In AML, a high cellular density of CD30L was detected in French-American-British M3, M4, and M5 phenotypes, which are directly associated with the presence on tumor cells of certain surface structures, including the p55 interleukin-2 receptor alpha-chain, the alpha(M) (CD11b) chain of beta2 integrins, and the intercellular adhesion molecule-1 (CD54). Analysis of normal hematopoietic cells evidenced that, in addition to circulating and tonsil B cells, a fraction of bone marrow myeloid precursors, erythroblasts, and subsets of megakaryocytes also express CD30L. Finally, we have shown that native CD30L expressed on primary leukemic cells is functionally active by triggering both mitogenic and antiproliferative signals on CD30+ target cells. As opposed to CD30L, only 10 of 181 primary tumors expressed CD30 mRNA or protein, rendering therefore unlikely a CD30-CD30L autocrine loop in human hematopoietic neoplasms. Taken together, our data indicate that CD30L is widely expressed from early to late stages of human hematopoiesis and suggest a regulatory role for this molecule in the interactions of normal and malignant hematopoietic cells with CD30+ immune effectors and/or microenvironmental accessory cells.

5/3,AB/50 (Item 50 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

09216480 96293400 PMID: 8700513

S-phase induction by adenovirus E1A requires activation of cdc25a tyrosine phosphatase.

Spitkovsky D; Jansen-Durr P; Karsenti E; Hoffman I

Angewandte Tumorforschung, Deutsches Krebsforschungszentrum, Germany.

Oncogene (ENGLAND) Jun 20 1996, 12 (12) p2549-54, ISSN 0950-9232

Journal Code: ONC

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Adenovirus E1A proteins can induce quiescent cells to enter S-phase and

also affect the expression of cellular genes including various cell cycle regulators. Here we show that human cdc25A, a tyrosine phosphatase involved in regulation of the G1/S-phase transition of the cell cycle, is a target of the adenovirus E1A protein in virus-infected human fibroblasts. Expression of E1A in quiescent fibroblasts leads to a rapid increase in cdc25A phosphatase activity and also increases both cdc25A and cyclin E gene expression. Inhibition of cdc25A function by antibody injection prevents virus-induced entry into S-phase. These results indicate that induction of high levels of cdc25A and its potential positive regulator cyclin E mediates the ability of E1A to induce S-phase in the presence of antiproliferative signals.

5/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

08925196 96249501 PMID: 8668914
Triggering of target of an antiproliferative antibody-
1 (TAPA-1/CD81) up-regulates the release of tumour
necrosis factor-alpha by the EBV-B lymphoblastoid cell line JY.
Altomonte M; Montagner R; Pucillo C; Maio M
Advanced Immunotherapy Unit, INRCCS-CRO, Department of Sciences and
Biomedical Technologies, University of Udine, Italy.
Scandinavian journal of immunology (ENGLAND) Apr 1996, 43 (4)
p367-73, ISSN 0300-9475 Journal Code: UCW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Target of an antiproliferative antibody-1 (TAPA-1/CD81) has been shown to be non-covalently associated to HLA-DR antigens on the cell surface of B cells. In this study the authors report that triggering of CD81 by MoAb 5A6 or 1D6 significantly ($P < 0.05$) up-regulates the release of tumour necrosis factor-alpha (TNF-alpha) by the Epstein-Barr virus-positive (EBV)-B lymphoblastoid cell line JY. The accumulation of TNF-alpha in the culture medium of JY cells incubated with either anti-CD81 MoAb was found to be dose-dependent and similar to that obtained following crosslinking of HLA-DR antigens with MoAb L243. The effect of the combination of anti-CD81 and anti-HLA-DR MoAb on the release of TNF-alpha by JY cells was not synergistic or additive. In addition, the combination of anti-CD81 and anti-HLA-DR MoAb did not affect proliferation and homotypic aggregation of JY cells induced by each MoAb used alone. Both anti-CD81 or anti-HLA-DR MoAb induced protein tyrosine phosphorylation. However, different cytoplasmic proteins were phosphorylated following triggering of either molecule. Taken together, the data demonstrate that CD81 and HLA-DR antigens induce similar effector phenomena in the regulation of TNF-alpha release, homotypic aggregation and inhibition of JY cell proliferation.

5/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

08859544 94334728 PMID: 8057149
Effect of tyrphostin on cell growth and tyrosine kinase activity of epidermal growth factor receptor in human gliomas.
Miyaji K; Tani E; Shindo H; Nakano A; Tokunaga T
Department of Neurosurgery, Hyogo College of Medicine, Japan.
Journal of neurosurgery (UNITED STATES) Sep 1994, 81 (3) p411-9,
ISSN 0022-3085 Journal Code: JD3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The effects of tyrphostin, a selective protein tyrosine kinase

inhibitor, on epidermal growth factor (EGF)-stimulated cell growth and EGF-receptor tyrosine kinase activity were studied in four human glioma cell lines. Stimulation by EGF induced variable enhancements of cell growth as well as tyrosine phosphorylation of EGF receptor and intracellular **target** proteins in all glioma cell lines. The level of immunoreactive EGF receptor detected with antibodies against extra- and intracellular domains was moderate in all four glioma cell lines, but markedly decreased with the latter **antibody** in two glioma cell lines. This variation was associated with considerable reduction of the EGF-stimulated tyrosine autophosphorylation level. Tyrphostin **inhibited** dose-dependently the EGF-stimulated cell growth and tyrosine autophosphorylation in all glioma cell lines, and the optimum time for the maximum **inhibitory** effect on tyrosine autophosphorylation was 12 to 18 hours after treatment with tyrphostin. The **antiproliferative** activity of tyrphostin nearly correlated quantitatively with its potency as an **inhibitor** of the EGF-stimulated EGF receptor tyrosine kinase activity. Tyrphostin had no significant effect on the immunoreactive EGF receptor levels, on the affinity constants and numbers of EGF receptor, or on the down-regulation and specific internalization of EGF receptor in any glioma cell line, suggesting that the effects of tyrphostin are not likely to be the results of reduction in EGF receptor and EGF binding capacity. In addition, the serum-stimulated cell growth was also **inhibited** dose-dependently by higher concentrations of tyrphostin in all glioma cell lines. It might be suggested, therefore, that tyrphostin **inhibits** EGF-stimulated cell growth by a specific suppression of EGF receptor tyrosine kinase activity, and at higher concentrations there appears to be some degree of either nonspecific **inhibition** or **inhibition** of serum-stimulated protein tyrosine kinase activity to induce the cell growth **inhibition** of gliomas.

5/3,AB/53 (Item 53 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08801246 96042117 PMID: 7595190

Engaging CD19 or **target** of an **antiproliferative antibody 1** on human B lymphocytes induces binding of B cells to the interfollicular stroma of human tonsils via integrin alpha 4/beta 1 and fibronectin.

Behr S; Schriever F
Department of Hematology and Oncology, Virchow University Hospital, Humboldt University Berlin, Germany.

Journal of experimental medicine (UNITED STATES) Nov 1 1995, 182 (5) p1191-9, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Adhesion of B lymphocytes within the different compartments of secondary lymphoid organs is essential for the function of the humoral immune response. It is not currently known how the temporary immobilization of B cells in distinct areas of this complex microenvironment is regulated. The present study aimed at defining B cell antigens that initiate binding of B cells to human tonsil sections *in situ*. Engaging the B cell antigens CD19 and **target** of an **antiproliferative antibody 1** (

TAPA-1) with monoclonal antibodies induced adhesion of these B cells to the interfollicular stroma. This binding occurred through the integrin alpha 4 beta 1 on the B cell surface and via the extracellular matrix protein fibronectin expressed in the interfollicular compartment of the tonsil. Signaling through either antigen, CD19 or **TAPA-1**, depended on tyrosine kinases. Binding induced by engaging CD19 required an intact cytoskeleton, whereas **TAPA-1**-transmitted adhesion did not. We suggest that CD19 and **TAPA-1** have a novel and unique function by regulating an alpha 4 beta 1/fibronectin-mediated binding of B cells to the interfollicular stroma of

lymphoid tissues.

5/3,AB/54 (Item 54 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08774233 95363088 PMID: 7636191

Molecular analyses of the association of CD4 with two members of the transmembrane 4 superfamily, **CD81** and **CD82**.

Imai T; Kakizaki M; Nishimura M; Yoshie O
Shionogi Institute for Medical Science, Osaka, Japan.

Journal of immunology (UNITED STATES) Aug 1 1995, 155 (3) p1229-39,
ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Previously, we have shown that **CD81** and **CD82**, two members of the transmembrane 4 superfamily, form multimolecular membrane complexes by associating with each other and with CD4 or CD8 in T cells. In the present study, we further analyzed the molecular basis of the CD4 association with **CD81** and **CD82** by co-precipitation experiments. First, we examined the regions of CD4 involved in the association with **CD81** and **CD82** by employing chimeric proteins generated from CD4 and CD2. It was confirmed that CD4, but not CD2, was capable of binding with **CD81** and **CD82** in transfected cells. We found that the cytoplasmic region of CD4 was sufficient for the chimeric proteins to co-precipitate **CD81**, while both the cytoplasmic and extracellular regions of CD4 were required for them to efficiently co-precipitate **CD82**. We next found, by using truncated CD4 lacking the C-terminal 31 amino acids or mutated CD4 with the cysteine residues at 394 and 397 replaced by serine, that the p56lck binding site or the covalent modification with palmitic acid was not necessary for CD4 to associate with **CD81** and **CD82**. Finally, we found that the binding of p56lck to CD4 strongly inhibited its association with **CD81** and **CD82**. It is, therefore, suggested that CD4 exists at least in two physical states, one associated with p56lck and another associated with **CD81** and **CD82** in the absence or uncoupling of p56lck.

5/3,AB/55 (Item 55 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08550213 95325577 PMID: 7602090

CD82, member of the tetra-span-transmembrane protein family, is a costimulatory protein for T cell activation.

Lebel-Binay S; Lagaudriere C; Fradelizi D; Conjeaud H
Immunomodulation and Autoimmunity Laboratory, Rene Descartes University, Cochin Hospital, Paris, France.

Journal of immunology (UNITED STATES) Jul 1 1995, 155 (1) p101-10,
ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH
Document type: Journal Article
Record type: Completed
It is now well documented that full activation of T cells requires a two-signal triggering that can be mimicked, in the absence of accessory cells, by co-immobilization of mAbs directed to stimulatory/accessory molecules (CD2, CD3, CD28, adhesion molecules, etc.). In this report, we describe that engagement of CD82 can deliver such a costimulatory signal for full activation of the human T cell line Jurkat, leading to strong IL-2 production and cell differentiation. The CD82 Ag, which belongs to the new tetra-span-transmembrane family (CD9, CD37, CD53, CD63, and **CD81** (**TAPA-1**)), has been identified originally in our laboratory for its enhanced expression on three LAK-susceptible cell lines, and has been characterized as an activation/differentiation marker of mononuclear cells. Jurkat cells, stimulated in vitro by co-immobilization of anti-CD82 and

anti-CD3 mAbs, produced high levels of IL-2, became strongly adherent to plastic dishes, and developed dendritic processes. These morphologic changes, associated with a total arrest of cell proliferation, were not the result of cell death but rather of cell differentiation, as shown by an increase in their metabolic activity. Costimulation through both CD82 and CD3 induced up-regulation of both IL-2 and IFN-gamma mRNA synthesis (but not of IL-4) and an increased expression of HLA class I molecules at the cell surface, which was **inhibited** by anti-IFN-gamma Ab.

5/3,AB/56 (Item 56 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08292908 95070183 PMID: 7979417
Relationship between **antiproliferative** activity of acetylenic alcohol, panaxydol, and its affinity for **target** cell membrane]
Matsunaga H; Saita T; Nagumo F; Mori M; Katano M
Dept. of Hospital Pharmacy, Saga Medical School.
Gan to kagaku ryoho (JAPAN) Nov 1994, 21 (15) p2585-9, ISSN 0385-0684 Journal Code: 6T8
Languages: JAPANESE
Document type: Journal Article
Record type: Completed
Acetylenic alcohol, panaxydol, isolated from Panax ginseng shows a significant growth **inhibitory** effect against various types of cultured cell lines. Its anti-proliferative effect is highly specific for malignant cells, but varies by cell lines. In the present study, the relationship between cellular sensitivity to panaxydol and the affinity of panaxydol for **target** cells was studied. Panaxydol was conjugated to bovine serum albumin (BSA). Panaxydol-BSA was first incubated with sensitive cells, MK-1 cells, or resistant cells, HeLa cells, and then FITC-labeled anti-BSA **antibody** was added. The percentage of labeled cells and relative mean of fluorescence were determined by flow cytometry. The results indicate that the sensitivity of **target** cells against panaxydol is partly prescribed by its affinity for **target** cells.

5/3,AB/57 (Item 57 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08186403 94292501 PMID: 8021251
The 86-kDa subunit of autoantigen Ku is a somatostatin receptor regulating protein phosphatase-2A activity.
Le Romancer M; Reyl-Desmars F; Cherifi Y; Pigeon C; Bottari S; Meyer O; Lewin MJ
Unite de Recherches de Gastroenterologie, INSERM U10, Hopital Bichat-Claude Bernard, Paris, France.
Journal of biological chemistry (UNITED STATES) Jul 1 1994, 269 (26) p17464-8, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We previously reported the immunopurification of a somatostatin receptor from the human tumoral gastric cell HGT1 using the monoclonal **antibody** 30F3 (Reyl-Desmars, F., Le Roux, S., Linard, C., Benkouka, F., and Lewin, M. J. M. (1989) J. Biol. Chem. 264, 18789-18795). Screening of a lambda gt11 HGT1-cDNA library with 30F3 led us to isolate a cDNA encoding an 86-kDa polypeptide displaying 100% structural identity with the 86-kDa subunit (p86-Ku) of the Ku autoantigen. Recombinant p86 expressed in Escherichia coli cross-reacted with 30F3 and specifically bound [¹²⁵I-Tyr11]somatostatin-14. Binding was totally displaced by somatostatin-14, somatostatin-28, and SMS 201-995, with IC₅₀ values of 0.7, 1.0, and 1.2 nM, respectively. In a search for a biological effect associated with binding, we purified a 36-kDa, okadaic

acid-sensitive phosphatase (protein phosphatase-2A (PP2A)) from rat gastric cytosol. PP2A catalyzed 32P release from p34cdc2-phosphorylated histone H1. However, PP2A-induced 32P release was concentration dependently inhibited by recombinant p86-Ku, with a decrease in maximal velocity without a change in Km. Steric exclusion high pressure chromatography indicated that the inhibition resulted from direct interaction of the enzyme with p86-Ku. Furthermore, it was antagonized by increased concentrations of somatostatin-14 and prevented by preincubating p86-Ku with 30F3. Given the key role played by PP2A in cell cycle regulation, the current findings suggest that p86-Ku could be a physiological target of somatostatin antiproliferative action.

5/3,AB/58 (Item 58 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

08159926 94242864 PMID: 8186325

Antiproliferative lymphokine production by human peripheral blood lymphocytes and lymph node lymphocytes detected by a modified double layer soft agarose clonogenic assay.

Saito T; Okadome M; Sugihara K; Sano M; Kamura T; Nakano H
Department of Gynecology and Obstetrics, Faculty of Medicine, Kyushu University, Fukuoka, Japan.

Lymphokine and cytokine research (UNITED STATES) Feb 1994, 13 (1)
p55-62, ISSN 1056-5477 Journal Code: A3G

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The double layer soft agarose clonogenic assay using colony formation of target cells as an endpoint was adapted for the detection of antiproliferative lymphokine production from peripheral blood lymphocytes (PBL) and lymph node lymphocytes (LNL). The colony formation of cervical cancer cell lines, HeLa, CAC-1, and TMCC, in the upper layers was significantly inhibited by the inclusion of either PBL or LNL pretreated with PHA in the lower layers. Without stimulation by PHA, neither resident PBL nor LNL exhibited antiproliferative activity on the tumor cells in the upper layers. The antiproliferative activity against target cells increased in relation to the density of lymphocytes in the lower layers, and was dependent on protein synthesis by lymphocytes. Since the cell to cell contact between the effector cells and target cells is not possible in this assay, the reduction of colony formation should be attributed to soluble factor(s) that were secreted from the lymphocytes. Additionally, an antibody against IFN-gamma neutralized most of the antiproliferative activity, and equivalent levels of IFN-gamma were found to be present in the supernatant of PBL and LNL lower layers by a radioimmunoassay. The double layer soft agarose assay system should thus serve as a useful method for studying antiproliferative lymphokine production by lymphocytes.

5/3,AB/59 (Item 59 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

07963227 94065201 PMID: 8245480

C33 antigen and M38 antigen recognized by monoclonal antibodies inhibitory to syncytium formation by human T cell leukemia virus type 1 are both members of the transmembrane 4 superfamily and associate with each other and with CD4 or CD8 in T cells.

Imai T; Yoshie O

Shionogi Institute for Medical Science, Osaka, Japan.

Journal of immunology (UNITED STATES) Dec 1 1993, 151 (11) p6470-81,
ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: Journal Article

Record type: Completed
C33 Ag and M38 Ag had been identified by mAb **inhibitory** to HTLV-1-induced syncytium formation. The cDNA encoding C33 Ag had revealed that it belongs to the newly defined transmembrane 4 superfamily (TM4SF). M38 Ag was detected on virtually all human cell lines and fresh leukocytes except for most granulocytes. It was also expressed on a mouse hybrid cell clone containing human chromosome 11q23-pter. Immunoprecipitation and immunoblot analyses identified a monomeric 26-kDa protein. The M38 epitope was dependent on S-S bonding. These characteristics were very similar to those reported for **TAPA-1** (the **target** of **antiproliferative antibody-1**), which also belongs to TM4SF as C33 Ag. We therefore cloned the cDNA of human **TAPA-1** and expressed it in COS cells. M38 indeed reacted with COS cells expressing human **TAPA-1**. We concluded that M38 Ag was identical to **TAPA-1**. To further investigate the biologic functions of C33 Ag and M38 Ag (**TAPA-1**) and their roles in HTLV-1-induced syncytium formation, molecules associated with these Ag were examined in T cells. Immunoprecipitation from surface-iodinated cell lysates revealed that proteins co-precipitated by C33 and M38 were mostly common including each other. Sequential immunoprecipitation-immunoblot experiments confirmed that C33 Ag and M38 Ag (**TAPA-1**) were associated with each other. The association was further confirmed in BHK cells doubly transfected with human cDNA for C33 Ag and **TAPA-1**. We extended similar analyses and found that C33 Ag and M38 Ag (**TAPA-1**) were regularly associated with CD4 or CD8. The association of these Ag on the cell surface was further supported by co-modulation of M38 Ag (**TAPA-1**), CD4 and CD8 with C33 Ag. This is the first time that a physical association between the members of TM4SF is demonstrated. Furthermore, the regular association of C33 Ag and M38 Ag (**TAPA-1**) with CD4 or CD8 might indicate that they play a role in expression and/or function of the CD4/CD8 co-receptor complex.

5/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07911617 93150536 PMID: 8381244

Augmented **inhibition** of MethA tumor cell proliferation in combined use of diethyldithiocarbamate with catalase or by a nondialysable fraction from co-incubation.

Mashiba H; Matsunaga K
Division of Immunology, National Kyushu Cancer Center, Fukuoka, Japan.
Toxicology letters (NETHERLANDS) Jan 1993, 66 (1) p97-104, ISSN 0378-4274 Journal Code: VZN

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The **antiproliferative** effect of diethyldithiocarbamate (DDC), a metal chelator, in combined use with catalase on MethA tumor cells was studied. Marked augmentation of the **antiproliferative** effect was observed when 1×10^{-7} M DDC was used in combination with catalase (0.004-40 micrograms/ml). Further augmentation of the cytostatic effect was obtained by the simultaneous addition of 2×10^{-7} M DDC with catalase and more than 97% **inhibition** of [³H]thymidine uptake by **target** cells was observed. A nondialysable fraction from the co-incubation of DDC with catalase was also remarkably cytostatic to the **target** cells. Serum factor(s), probably metal ions, was suggested to be necessary for the induction of the nondialysable fraction with cytostatic activity. The activity was not nullified by the pretreatment of a nondialysable fraction with anti-catalase **antibody**. These results suggest that an active substance or compound exhibiting an **antiproliferative** effect on tumor cells might be newly formed as the result of the interaction of DDC with catalase.

5/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07752195 93017895 PMID: 1383329

The CD19/CD21 signal transducing complex of human B lymphocytes includes the target of antiproliferative antibody-1 and Leu-13 molecules.

Bradbury LE; Kansas GS; Levy S; Evans RL; Tedder TF
Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston, MA 02115-6084.

Journal of immunology (UNITED STATES) Nov 1 1992, 149 (9) p2841-50,
ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI-26872, AI, NIAID; CA-34183, CA, NCI; CA-54464, CA, NCI; +

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD19 is a member of the Ig superfamily expressed on the surface of B lymphocytes that may be involved in the regulation of B cell function. Immunoprecipitation studies with B cell lines solubilized by digitonin have shown CD19 to be part of a multimolecular complex that includes CD21 (CR2) and other unidentified proteins. In this study, two of the CD19-associated proteins were identified as **TAPA-1**, which is expressed on most cell types, and Leu-13, which is expressed on subsets of lymphoid cells. **TAPA-1** and Leu-13 are physically associated in many cell lineages. CD19 and CD21 mAb each specifically coprecipitated proteins of the same size as those precipitated by **TAPA-1** and Leu-13 mAb from B cell lines and cDNA-transfected K562 cell lines. Western blot analysis with a **TAPA-1** mAb verified the identity of **TAPA-1** in CD19 and CD21 immunoprecipitated materials. In addition, when **TAPA-1** or Leu-13 were crosslinked and patched on the cell surface, all of the CD19 comigrated with **TAPA-1** and some of the CD19 comigrated with Leu-13. Furthermore, mAb binding to CD19, CD21, **TAPA-1**, and Leu-13 on B cell lines induced similar biologic responses, including the induction of homotypic adhesion, inhibition of proliferation, and an augmentation of the increase in intracellular [Ca²⁺] induced by suboptimal cross-linking of surface Ig on B cell lines. Together, these data suggest that **TAPA-1** and Leu-13 are broadly expressed members of a signal transduction complex in which lineage-specific proteins, such as CD19 and CD21, provide cell-specific functions.

5/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07646344 93017900 PMID: 1401919

C33 antigen recognized by monoclonal antibodies inhibitory to human T cell leukemia virus type 1-induced syncytium formation is a member of a new family of transmembrane proteins including CD9, CD37, CD53, and CD63.

Imai T; Fukudome K; Takagi S; Nagira M; Furuse M; Fukuhara N; Nishimura M; Hinuma Y; Yoshie O

Shionogi Institute for Medical Science, Osaka, Japan.

Journal of immunology (UNITED STATES) Nov 1 1992, 149 (9) p2879-86,
ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

C33 Ag was originally identified by mAb inhibitory to syncytium formation induced by human T cell leukemia virus type 1. The Ag was shown to be a highly heterogeneous glycoprotein consisting of a 28-kDa protein and N-linked oligosaccharides ranging from 10 to 50 kDa. In the present study, cDNA clones were isolated from a human T cell cDNA expression

library in Escherichia coli by using mAb C33. The identity of cDNA was verified by immunostaining and immunoprecipitation of transfected NIH3T3 cells with mAb. The cDNA contained an open reading frame of a 267-amino acid sequence which was a type III integral membrane protein of 29.6 kDa with four putative transmembrane domains and three putative N-glycosylation sites. The C33 gene was found to belong to a newly defined family of genes for membrane proteins, such as CD9, CD37, CD53, CD63, and **TAPA-1**, and was identical to R2, a cDNA recently isolated because of its strong up-regulation after T cell activation. Availability of mAb for C33 Ag enabled us to define its distribution in human leukocytes. C33 Ag was expressed in CD4+ T cells, CD19+ B cells, CD14+ monocytes, and CD16+ granulocytes. Its expression was low in CD8+ T cells and mostly negative in CD16+ NK cells. PHA stimulation enhanced the expression of C33 Ag in CD4+ T cells by about 5-fold and in CD8+ T cells by about 20-fold. PHA stimulation also induced the dramatic size changes in the N-linked sugars previously shown to accompany human T cell leukemia virus type 1-induced transformation of CD4+ T cells.

5/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07553889 92078843 PMID: 1720807

Identification of the motility-related protein (MRP-1), recognized by monoclonal **antibody** M31-15, which **inhibits** cell motility.

Miyake M; Koyama M; Seno M; Ikeyama S

Department of Thoracic Surgery, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan.

Journal of experimental medicine (UNITED STATES) Dec 1 1991, 174 (6) p1347-54, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

A murine monoclonal **antibody** (M31-15) was identified using the penetration-**inhibiting** assay of a human lung adenocarcinoma cell line (MAC10) and remarkably **inhibited** the phagokinetic tract motility of various cancer cell lines. The antigen, motility-related protein (MRP-1), recognized by M31-15, was 25- and 28-kD proteins, and M31-15 was used to isolate a cDNA clone from a human breast carcinoma cDNA library. Sequence analysis revealed that MRP-1 had strong similarity with a B cell surface antigen (CD37), a melanoma-associated antigen (ME491), the target of an **antiproliferative antibody** (**TAPA-1**), a human tumor-associated antigen (CO-029), and the Sm23 antigen of the trematode parasite Schistosoma mansoni.

5/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07532643 91370732 PMID: 1654145

Attempt to augment the anti-proliferative effect of recombinant human lymphotoxin in combined use with anti-tumor **antibody**-diethyldithiocarbamate conjugates.

Mashiba H; Matsunaga K

Division of Immunology, National Kyushu Cancer Center, Fukuoka, Japan.

European cytokine network (FRANCE) May-Jun 1991, 2 (3) p195-9, ISSN 1148-5493 Journal Code: A56

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We have attempted to augment specifically the **antiproliferative** effect of recombinant human lymphotoxin (rhLT) on tumor cells in combined use with diethyldithiocarbamate (DDC) which is known to inactivate superoxide dismutase. For this purpose, anti-Meth A tumor cell

antibody -DDC conjugates were used to confer the selectivity on the augmented **antiproliferative** effect in combined use of rhLT with DDC. Simultaneous addition of rhLT (1 u/ml to 100 u/ml) with the diluted conjugates to the **target** Meth A tumor cells induced the augmentation of the **antiproliferative** effect although **antibody** control was not effective. Similar augmentation of the **antiproliferative** effect was obtained when the **target** cells were treated with the conjugates prior to the addition of rhLT although the rate of **inhibition** was low. This approach seems to be useful because the **antiproliferative** effect of LT on **target** tumor cells could be augmented and side effects of LT could be avoided.

5/3,AB/65 (Item 65 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

07530247 91318144 PMID: 1650385
Genomic organization and chromosomal localization of the **TAPA-1** gene.
Andria ML; Hsieh CL; Oren R; Francke U; Levy S
Department of Medicine/Oncology, Stanford University School of Medicine, CA.
Journal of immunology (UNITED STATES) Aug 1 1991, 147 (3) p1030-6,
ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI07290, AI, NIAID; CA34233, CA, NCI; GM26105, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
TAPA-1 is a 26-kDa integral membrane protein expressed on many human cell types. Antibodies against **TAPA-1** induce homotypic aggregation of cells and can **inhibit** their growth. The murine homologue of **TAPA-1** was cloned from both cDNA and genomic DNA libraries. A very high level of homology was found between human and mouse **TAPA-1**. The 5' untranslated region of the **TAPA-1** gene resembles housekeeping gene promoters with respect to G + C content and the presence of potential Sp1 binding sites. The chromosomal localization of human and murine **TAPA-1** genes was determined by Southern blot experiments using DNA from somatic cell hybrids. The genes were found to be part of a conserved syntenic group in mouse chromosome 7 and the short arm of human chromosome 11. The organization of the **TAPA-1** gene and the projection of the exon boundaries on the proposed protein structure are presented.

5/3,AB/66 (Item 66 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

07249974 90375917 PMID: 2398277
TAPA-1, the **target** of an **antiproliferative antibody**, is associated on the cell surface with the Leu-13 antigen.
Takahashi S; Doss C; Levy S; Levy R
Department of Medicine/Oncology, Stanford University Medical Center, CA 94305.
Journal of immunology (UNITED STATES) Oct 1 1990, 145 (7) p2207-13,
ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: CA 34233, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A murine mAb, 5A6 (IgG1), has been isolated by immunization with a human B lymphoma cell line and screening for growth **inhibition**. The **antibody** immunoprecipitated a single chain protein of 26 kDa from cell lysates made with Triton X-100 but additional proteins were

precipitated when cell lysates were made with the milder detergent CHAPS (3-[3-cholamidopropyl]dimethylammonio)-1-propane sulfate). We have identified one of these coprecipitated molecules as the 16-kDa Leu-13 Ag. 5A6 and anti-Leu-13 showed similar, although not identical, reactivity, growth inhibition and temperature-dependent aggregation effects among hematolymphoid cell lines. The aggregation induced by 5A6 and anti-Leu-13 was not dependent on LFA-1 (lymphocyte function-associated Ag-1). The cell-surface expression of both **TAPA-1** (target of an antiproliferative antibody-1) and Leu-13 could be down-modulated by binding to their respective antibodies and they could be reciprocally comodulated. These results suggest that **TAPA-1** and Leu-13 form a complex on the cell surface and play a role in growth control through a common pathway.

5/3,AB/67 (Item 67 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

07144270 93389121 PMID: 7690791

The CD19 signal transduction complex of B lymphocytes. Deletion of the CD19 cytoplasmic domain alters signal transduction but not complex formation with **TAPA-1** and Leu 13.

Bradbury LE; Goldmacher VS; Tedder TF
Division of Tumor Immunology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115-6084.
Journal of immunology (UNITED STATES) Sep 15 1993, 151 (6) p2915-27,
ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI-26872, AI, NIAID; CA-34183, CA, NCI; CA-54464, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

CD19 expressed on the surface of B lymphocytes is a key member of a cell surface signal transduction complex that includes **TAPA-1**, Leu 13 and CD21. The human CD19 protein is composed of 540 amino acids with a cytoplasmic domain of 242 amino acids. Although the cytoplasmic domain of CD19 has no sequence homology with other proteins, the cytoplasmic domain of human, mouse, and guinea pig CD19 is highly conserved suggesting that this region of CD19 is at least partially responsible for signaling activity. In this study, the regions of CD19 required for intermolecular associations and signal transduction were determined by comparing a series of carboxyl-terminal cytoplasmic tail deletion mutants and a CD19/L-selectin chimera with native CD19. CD19 expressed in the human Rex T cell line and the K562 erythroleukemia cell line generated transmembrane signals and also associated with endogenous **TAPA-1**. Deletion of 95% of the CD19 cytoplasmic domain did not affect the ability of CD19 to be expressed or to associate with **TAPA-1**. However, replacement of the CD19 transmembrane and cytoplasmic domains with those of L-selectin (CD19-LAM) resulted in the loss of CD19 complex formation, suggesting that the membrane spanning domain is critical for this association. Similarly, the induction of homotypic adhesion through CD19 or truncated CD19 was equivalent, whereas homotypic adhesion was not induced via the CD19-LAM chimera. In addition, the cytoplasmic domain was not necessary for CD19 mAb-mediated growth inhibition or internalization. In contrast, the CD19 cytoplasmic domain was required for optimal mAb-induced increases in $[Ca^{2+}]_i$ in CD19 cDNA-transfected Rex cells. Thus, the CD19 cytoplasmic domain is responsible for the induction of increased $[Ca^{2+}]_i$, and the transmembrane region is required for cell surface associations with the other members of the CD19 complex and most signaling events. Therefore, mAb binding to CD19 is likely to initiate multiple intracellular signal transduction cascades either through CD19 directly, or through other members of the CD19 complex.

5/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07141609 93346737 PMID: 7688390

Anti-**TAPA-1** antibodies induce protein tyrosine phosphorylation that is prevented by increasing intracellular thiol levels.

Schick MR; Nguyen VQ; Levy S

Department of Medicine, School of Medicine, Stanford University, CA 94305.

Journal of immunology (UNITED STATES) Aug 15 1993, 151 (4) p1918-25,
ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI-07290, AI, NIAID; CA 34233, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We studied the signal induced by the anti-**TAPA-1** antibody and compared it to the signal induced by anti-IgM antibodies in a human B cell line, OC1-LY8. We found that exposure of these cells to either antibody resulted in a rapid increase in protein tyrosine phosphorylation which was prevented by **inhibitors** of tyrosine kinases. Tyrosine phosphorylation was an early event in the cascade leading to the antiproliferative effect of the anti-**TAPA-1** antibody. However, 2-ME, a reducing agent that is not an **inhibitor** of tyrosine kinases, prevented both tyrosine phosphorylation and the antiproliferative effect of the antibody. Cells grown in low concentrations of 2-ME did not exhibit an increase in tyrosine phosphorylation in response to the anti-**TAPA-1** antibody and were insensitive to the antiproliferative effect of the antibody. In contrast, the same cells maintained in 2-ME were able to induce tyrosine phosphorylation in response to anti-IgM. The use of 2-ME resulted in an increase in intracellular thiols, mostly glutathione. Moreover, compounds that block glutathione synthesis rendered cells susceptible to the antibody, even in the presence of 2-ME. These experiments demonstrate that tyrosine kinases are involved in propagating the antiproliferative signal initiated by the anti-**TAPA-1** antibody and suggest that this signal is dependent upon the level of intracellular thiols.

5/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06922381 92167302 PMID: 1371549

ME491 melanoma-associated glycoprotein family: antigenic identity of ME491, NKI/C-3, neuroglandular antigen (NGA), and CD63 proteins.

Demetrick DJ; Herlyn D; Tretiak M; Creasey D; Clevers H; Donoso LA; Vennegoor CJ; Dixon WT; Jerry LM

Oncology Research Group, Faculty of Medicine, University of Calgary, Alberta, Canada.

Journal of the National Cancer Institute (UNITED STATES) Mar 18 1992,
84 (6) p422-9, ISSN 0027-8874 Journal Code: J9J

Contract/Grant No.: CA-10815, CA, NCI; CA-25874, CA, NCI

Erratum in J Natl Cancer Inst 1992 May 6;84(9) 727

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

BACKGROUND: Numerous monoclonal antibodies (MAbs) have been produced to antigens found in human melanomas. Three of the best characterized melanoma antigens include the melanoma-associated glycoproteins (MAGs) defined by two reagent families--the ME491 family (including ME491, 8-1H, and 8-2A) and the NKI/C-3 family (including NKI/C-3 and NKI/black-13)--as well as the neuroglandular antigen (NGA) defined by MAbs LS59, LS62, and LS140. These three antigens have significant similarities in tissue distribution, biosynthesis, and structure. The ME491 MAG has been cloned, mapped, and sequenced. Numerous non-melanoma-associated proteins (Sm23, CO-029, R2, **TAPA-1**, CD9, CD37, CD53, and CD63) have recently been shown to

have significant homology to this sequence. PURPOSE: We conducted this study to investigate the similarity between the two MAG antigens and NGA. METHODS: Several reagents defining the three different melanoma antigens were compared, using competition immunoprecipitation, immunoassay, and inhibition radioimmunoassay techniques. RESULTS: Immunoassay experiments show that MAbs defining the three melanoma antigens bind to affinity-purified ME491 antigen and inhibit each other from binding in an inhibition radioimmunoassay. Competition immunoprecipitation experiments demonstrate that the ME491 and NKI/C-3 antibodies bind to NGA. Rabbit anti-ME491 idiotype serum recognizes determinants shared by NKI/C-3 and the anti-NGA MAbs. A competition immunoprecipitation experiment also confirms the identity of CD63, as defined by MAb RUU-SP 2.28, with the three melanoma antigens. CONCLUSION: These data indicate that the MAGs defined by ME491 and NKI/C-3 as well as the anti-NGA antibodies are epitopes of the same molecule, which is identical to CD63 by both immunochemical and molecular genetic investigations. IMPLICATIONS: Our results indicate that the data obtained in studies of these three melanoma antigens may be pooled, and we propose that the molecule recognized by these reagents be classified as CD63.

5/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

06140574 85081391 PMID: 3871222

Natural killing target antigens as inducers of interferon: studies with an immunoselected, natural killing-resistant human T lymphoblastoid cell line.

Howell DN; Andreotti PE; Dawson JR; Cresswell P
Journal of immunology (UNITED STATES) Feb 1985, 134 (2) p971-6,

ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: 5 T32 GM07171, GM, NIGMS; AI-14016, AI, NIAID; AI-15775, AI, NIAID

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The human T lymphoblastoid cell line CEM was subjected to immunoselection by co-culture with peripheral blood mononuclear cells (PBMC) for resistance to natural killer (NK) cell-mediated lysis. The NK susceptibility of the resulting subline, CEM.NKR, was 8.4 to 20.6% of that of CEM when PBMC or adherent cell-depleted PBMC were used as effector cells, and -7.1 to 12.1 % of that of CEM when Percoll gradient-enriched large granular lymphocytes (LGL) were used. However, CEM and CEM.NKR exhibited comparable sensitivity to antibody-dependent cellular cytotoxicity. Unlabeled CEM was eight- to 32-fold more effective than unlabeled CEM.NKR in inhibiting the NK lysis of labeled CEM target cells, and CEM bound 1.9 to 3.9-fold more Percoll gradient-enriched LGL than CEM.NKR in single cell-binding assays, suggesting that the NK-resistant variant has lost the expression of NK target antigens. However, CEM.NKR was comparable to CEM in its ability to induce interferon (IFN)-alpha production by PBMC in vitro, and the NK-resistant variant maintained its susceptibility to the antiproliferative effects of IFN-alpha, indicating that these phenomena may be mediated by molecules other than NK target structures. Comparison of CEM and CEM.NKR by indirect immunofluorescence with monoclonal antibodies specific for leukocyte antigens and the transferrin receptor, and by microcytotoxicity typing for HLA-A and B specificities, revealed no major differences.

5/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

06026440 89147517 PMID: 3265834

Growth effects of epidermal growth factor (EGF) and a monoclonal

antibody against the EGF receptor on four glioma cell lines.

Werner MH; Humphrey PA; Bigner DD; Bigner SH
Preuss Laboratory for Brain Tumor Research, Duke University Medical Center, Durham, NC 27710.

Acta neuropathologica (GERMANY, WEST) 1988, 77 (2) p196-201, ISSN 0001-6322 Journal Code: ICE
Contract/Grant No.: CA-11898, CA, NCI; CA-43722, CA, NCI; NS-20023, NS, NINDS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Epidermal growth factor (EGF) has been shown to stimulate DNA synthesis and cell division in normal glia. At least half of malignant human gliomas (MHG) express high levels of the EGF receptor (EGFR), which are above those detected in normal brain. The demonstration that antibodies against the EGFR **inhibit** the growth of squamous cell carcinoma line A-431, with large numbers of EGFR, *in vitro* and *in vivo* raises the possibility that these agents could be used therapeutically against malignant human gliomas either alone or conjugated to other agents. We have measured the growth effects of EGF and an anti-EGFR monoclonal **antibody**, 528 (Ab-528), on four well-characterized human malignant glioma cell lines, D-263 MG, D-247 MG, U-343 MGA Cl 2:6, and D-37 MG, with $2.9 \times 10(4)$, $1.5 \times 10(5)$, $8.6 \times 10(5)$ and $1.59 \times 10(6)$ EGFRs per cell, respectively. EGF significantly increased cell number in D-263 MG and D-37 MG by 65% and 74%, respectively, had no effect on D-247 MG, and significantly decreased cell number in U-343 MGA Cl 2:6 by 39%. U-343 MGA Cl 2:6 growth was **inhibited** 19% by Ab-528, but Ab-528 had no effect on growth of the other MHG lines. Ab-528 significantly **inhibited** all EGF-mediated growth effects. These studies demonstrate that, although Ab-528 alone has little **antiproliferative** activity on MHG, it successfully competes with EGF to reduce the biological effects of EGF-EGFR binding. Therefore, this **antibody** could potentially be used to **target** radioisotopes to MHG via the EGFR for diagnosis and therapy.

5/3,AB/72 (Item 1 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)

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13107862 BIOSIS NO.: 200100315011

Coupling the anti-neuroblastoma monoclonal **antibody** 15/7 with retinoic acid and testing the **antiproliferative** and differentiation effects of the immunoconjugate *in vitro* and *in vivo*.

AUTHOR: Voigt A(a); Schlick C(a); Zintl F(a)

AUTHOR ADDRESS: (a)Department of Pediatrics, University of Jena, Jena**
Germany

JOURNAL: Blood 96 (11 Part 1):p767a November 16, 2000

MEDIUM: print

CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000

SPONSOR: American Society of Hematology

ISSN: 0006-4971

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Because of the known property of spontaneous regression in neuroblastoma stage 4S all attempts are made to elucidate whether differentiation inducers could be used for neuroblastoma therapy. Here, we describe the coupling of the anti-neuroblastoma **antibody** 15/7 (moAb) with all-trans-retinoic acid (RA) for reducing the well known adverse effects of RA in treatment of neuroblastoma. The native moAb 15/7 was coupled by the EDC-(1-ethyl-3-(3-dimethylaminopropyl)carbodiimid-hydrochlorid) method. The

carbodiimide initially reacts with the available carboxyl group of RA to produce an active O-acylurea intermediate. This unstable intermediate reacts with the primary amine of the moAb to form an amide bond with the release of a soluble urea derivative to yield a RA-moAb-conjugate. The unbound RA was separated by gelfiltration. To examine the binding capacity of the structurally altered antibody the inhibition of proliferation was tested by means of 3-(4,5-dimethylthiazole-2-yl)-diphenyl tetrazolium bromide (MTT) and a cell-ELISA with target cells of the neuroblastoma cell line SK-N-MC. In both methods, no reduction of reactivity was observed in comparison with the unconjugated moAb. Therefore, we assumed that the coupling reaction did not change the variable region of the antibody for recognition the antigen. A model of metastatic neuroblastoma in SCID mice was established by injection of 2X10⁷ SK-N-MC cells per mouse. The administration of the conjugate (on average 16 mug RA bounded to 135 mug moAb) was performed six times every second day. As a result, the tumor mass per mouse was significantly reduced from 1.20 g to 0.32 g ($P < 0.001$) compared with control mice treated with unconjugated RA, moAb or NaCl. Similarly, the number of tumors per mouse and the average of weight per tumor were diminished after conjugate treatment in comparison with the NaCl-control group (67% and 40%, respectively). Antibodies that are involved in the differentiation of neuroblastoma (ICAM, NCAM, PECAM, TGF and NF-68) were bound more intensively to tumors of conjugate-treated mice. Our results suggest that RA-conjugated moAbs promote differentiation and inhibit proliferation in a more effective and specific manner than uncoupled RA as we have demonstrated in neuroblastoma. The use of RA-antibody-immunoconjugates could substitute the whole body therapy in RA treatment of neuroblastoma and leukemia because of the more favourable therapeutical drug dose to tumor cells.

2000

5/3,AB/73 (Item 2 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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13105148 BIOSIS NO.: 200100312297
Mechanism of hepatitis C virus-like particle-induced apoptosis in HUVEC.
AUTHOR: Munshi N(a); Ganju R K(a); Liang T Jake(a); Koziel M J(a); Groopman J E
AUTHOR ADDRESS: (a)Divisions of Experimental Medicine and Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA**USA
JOURNAL: Blood 96 (11 Part 1):p40a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Hepatitis C virus (HCV) infection causes inflammation of liver endothelium which contributes to the pathogenesis of chronic hepatitis. The mechanism of this endothelitis is not understood, since the virus does not appear to productively infect endothelial cells. We hypothesized an "innocent bystander" mechanism related to HCV proteins, and investigated whether the binding of HCV particles to human endothelium induced functional changes in the cells. Exposure of human vascular endothelial celis (HUVEC) to hepatitis C virus-like particles (HCV-LP) resulted in increased IL-8 production and induction of apoptosis. This

programmed cell death appeared to be mediated by the Fas/Fas-L pathway as neutralizing antibodies for Fas and Fas-L significantly protected HUVEC against HCV-LP induced apoptosis. Treatment of HUVEC with HCV particles also enhanced Fas-L expression in these cells and augmented caspase-3 activation. This was confirmed by using a specific caspase-3 inhibitor, Z-DEVD-FMK. Neutralizing antibody to the **CD81** receptor showed that it participated in the HCV particle induced apoptosis of endothelial cells. Release of interleukin-8 did not appear to involve the **CD81** receptor, and IL-8 did not modulate apoptosis as shown by blocking its cognate receptors on HUVEC. These results suggest that HCV envelope proteins can trigger the release of inflammatory chemokines and endothelial apoptosis, and may explain the pathological finding of endothelitis.

2000

5/3, AB/74 (Item 3 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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13082230 BIOSIS NO.: 200100289379
Identification and characterization of an ISG15 interacting protein,
9-27/Leu13.
AUTHOR: Chairatvit Kongthawat(a); Haas Arthur L(a)
AUTHOR ADDRESS: (a)Medical College of Wisconsin, 8701 Watertown Plank Road,
Milwaukee, WI, 53226**USA
JOURNAL: FASEB Journal 15 (4):pA514 March 7, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies
for Experimental Biology on Experimental Biology 2001 Orlando, Florida,
USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Interferon Stimulated Gene 15 protein (ISG15) is a member of the ubiquitin-like protein family. Yeast two-hybrid reveals that ISG15 interacts with the interferon inducible 1-8U protein, a member of the 1-8 family of proteins that include 1-8D and 9-27/Leu13. 9-27 is previously suggested to have an anti-proliferative activity in B-lymphocytes. Based on amino acid sequence conservation, we hypothesize that the 1-8 family acts as carrier proteins (E2) for ISG15 conjugation and that the anti-growth function of 9-27 requires its E2 activity. Purified recombinant flag-(9-27) protein **inhibits** growth of Daudi cells in a concentration-dependent manner ($K_d = 0.26 \pm 0.02$ mM) when measured by ^3H -thymidine incorporation. The anti-proliferative effect of flag-(9-27) is specific because the closely related recombinant flag-(1-8U) protein shows no anti-growth effect. Recombinant flag-(9-27)C84S, harboring a point mutation in the putative active site cysteine, shows no anti-proliferative activity even though it retains the affinity binding to Daudi cells ($K_i = 0.89 \pm 0.03$ mM). The growth **inhibition** of flag-(9-27) with $K_d=0.26 \pm 0.02$ suggests the binding to the membrane receptor of Daudi cells. Cross-linking experiments reveal that ISG15 is associated with 9-27/Leu13, as is **CD81/TAPA1** (a member of the tetraspannin superfamily of protein). This was further confirmed by *in vitro* binding of a major extracellular domain of **CD81** through the last 13 residues of flag-(9-27). Whether thiolester formation between ISG15 and 9-27 is required for the anti-proliferation is being investigated.

2001

5/3,AB/75 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13071637 BIOSIS NO.: 200100278786

The hepatitis C virus (HCV) induces a long-term increase of interleukin-10 production by human CD4+ T cells (H9).

AUTHOR: Delpuech Oona; Buffello-Le Guillou Delphine; Rubinstein Eric; Feray Cyrille; Petit Marie-Anne(a)

AUTHOR ADDRESS: (a)Centre Hepato-Biliaire, INSERM E. 99-41, Hopital Paul-Brousse, 12, Avenue Paul-Vaillant Couturier, 94800, Villejuif:
marie-anne@pbr.ap-hop-paris.fr**France

JOURNAL: European Cytokine Network 12 (1):p69-77 March, 2001

MEDIUM: print

ISSN: 1148-5493

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Patients with chronic hepatitis C present an imbalance of Th1/Th2 cytokine production. Therefore, we investigated whether the exposure of the CD4+ T cell line H9 to HCV could induce activation of cells through synthesis of IL-10. Three infection protocols were performed to enhance HCV propagation. Viral particles were prepared by ultracentrifugation of serum from patients. From 3 to 81 days post-infection (p.i.), HCV-RNA was monitored both in supernatants and cells by nested RT-PCR, IL-10 protein in medium by ELISA, and IL-10 mRNA in cells by semi-quantitative RT-PCR. The expression of tetraspanins was analyzed by flow cytometry. The PKC signal pathway was studied using specific **inhibitors**. The H9 cells express **CD81**. HCV-RNA (+) was detected in cells until 21 days p.i., and in culture media over 39 days p.i. Up to day 81 p.i., HCV exposure induced a specific, 2-fold increase of IL-10 production by H9 cells. IL-10 production was **inhibited** by a PKC **inhibitor** (Calphostin C). This study shows that even if the infection of H9 T cells did not result in any viral progeny, HCV induced the activation of IL-10 secretion, which supports the role of IL-10 in HCV pathogenesis.

2001

5/3,AB/76 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13067587 BIOSIS NO.: 200100274736

Inhibition of sperm-oolemma interactions by the extracellular domains of CD9 and **CD81**.

AUTHOR: Wong C H(a); Higginbottom A(a); Monk P(a); Partridge L J(a); Moore H D(a)

AUTHOR ADDRESS: (a)Department of Molecular Biology and Biotechnology, University of Sheffield, Western Bank, Sheffield, S10 2TN**UK

JOURNAL: Journal of Andrology (Supplement):p203 May-June, 2001

MEDIUM: print

CONFERENCE/MEETING: VIIth International Congress of Andrology Montreal, Canada June 15-19, 2001

ISSN: 0196-3635

RECORD TYPE: Citation

LANGUAGE: English

SUMMARY LANGUAGE: English

2001

5/3,AB/77 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12946922 BIOSIS NO.: 200100154071
Study of heparan sulfate-mediated binding of Hepatitis C virus on cells during in vitro infection.
ORIGINAL LANGUAGE TITLE: Etude du role des heparane sulfates dans l'etape initiale d'adsorption lors de l'infection cellulaire par le virus de l'hépatite C.
AUTHOR: Germi R(a); Crance J M(a); Drouet E(a); Guimet J(a); Lortat-Jacob H (a); Zarski J P(a); Jouan A(a); Garin D(a)
AUTHOR ADDRESS: (a)C.R.S.S.A., La Tronche, Grenoble**France
JOURNAL: Travaux Scientifiques des Chercheurs du Service de Sante des Armees (21):p65-66 2000
MEDIUM: print
ISSN: 0243-7473
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: French; Non-English
SUMMARY LANGUAGE: English; French

ABSTRACT: Two putative Hepatitis C virus (HCV) receptors have been identified: human **CD81** molecules and low-density lipoproteins receptor. This study shows that HCV and dengue virus binding on Vero cells can be **inhibited** by cellular heparan sulfates elimination using chemical or enzymatic treatment. Saturation of HCV binding sites by heparin could **inhibit** viral adsorption to. Therefore heparan sulfates could be a third HCV receptor.

DESCRIPTORS:
2000

5/3,AB/78 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12913693 BIOSIS NO.: 200100120842
Retinal pigment epithelium express **CD81** (target of the antiproliferative antibody).
AUTHOR: Geisert E E Jr(a); Abel H J; Fan L; Geisert G R
AUTHOR ADDRESS: (a)Univ Of Tennessee Hlth Sci Ctr, Memphis, TN**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7062
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The present study focuses on the role of **CD81** (the target of the antiproliferative antibody, TAPA) in the regulation of the growth of retinal pigment epithelium (RPE). RPE were cultured from eight-day old rat pups. The level of **CD81** in the cultures was defined by immunoblot methods and the distribution of the protein was examined using indirect immunohistochemical methods. In addition, the effects of the antibody binding were tested in culture. **CD81** was found in all layers of the normal retina with a distinct lack of labeling in the inner and outer segments of the photoreceptors. Based on our original immunohistochemical analysis (Clarke and Geisert, 1998 Mol. Vision,

<http://www.molvis.org/molvis/v4/a3/>), it was difficult to determine if **CD81** was expressed by RPE. By examining cultures of RPE we demonstrated that **CD81** was expressed on the surface of these cells and that it was concentrated at regions of cell-cell contact. When the AMP1 antibody (directed against the large extracellular loop of **CD81**) was added to cultured RPE the mitotic activity of the cells was depressed. Previous studies demonstrated that **CD81** was expressed in retinal glia, the Muller cells which span the thickness of the retina, and astrocytes found in the ganglion cell layer. The present study demonstrated that **CD81** was also expressed by RPE. The dramatic effects of the AMP1 antibody and the location of **CD81** at regions of cell-cell contact support the hypothesis that this molecule is part of a molecular switch controlling contact **inhibition**.

2000

5/3,AB/79 (Item 8 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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12869665 BIOSIS NO.: 200100076814
Intraparenchymal infusion of anti-TAPA/**CD81** antibodies leads to functional recovery after spinal cord injury.
AUTHOR: Hamers F P(a); Dijkstra S; Lankhorst A J; Joosten E A; Bar P R; Gispen W H; Geisert E E Jr
AUTHOR ADDRESS: (a)Rudolf Magnus Institute for Neurosciences, University Medical Center, Utrecht**Netherlands
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-18617
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Modulation of the glial response to spinal cord injury may lead to enhanced functional recovery. The monoclonal antibody AMP1 was found to alter the stability of astrocyte-astrocyte contact in vitro and to inhibit proliferation of astrocytes and microglia. Furthermore, the AMP1 antigen (TAPA/**CD81**) is upregulated after traumatic spinal cord injury. Therefore we studied whether intralesional infusion of AMP1-mAb could enhance functional recovery after spinal cord contusion injury. Female Wistar rats were subjected to a moderate spinal cord contusion injury and implanted at the lesion site with a stainless steel cannula connected to an osmotic minipump. Two different doses of AMP1-mAb and one dose of pre-immune IgG were infused for 14 days. Neurological function was regularly assessed on several function tests for 8 weeks. The lower dose of AMP1 led to significantly better function on BBB (+1.5 point) and Gridwalk tests as compared to the IgG control from 3 weeks onward. Hindpaw fine motor function, as assessed by BBB-subscores, was significantly better from 2 weeks onward. The higher dose of AMP1 did not differ from IgG control. These data suggest that AMP1 might be of value in the treatment of spinal cord injury, either by modulating the primary inflammatory process or by affecting the formation of the glial scar.

2000

5/3,AB/80 (Item 9 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)

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11919586 BIOSIS NO.: 199900165695

Transmembrane 4 superfamily protein CD151 (PETA-3) associates with betal and alphaIIIBbeta3 integrins in haemopoietic cell lines and modulates cell-cell adhesion.

AUTHOR: Fitter Stephen; Sincock Paul M; Jolliffe Corina N; Ashman Leonie K (a)

AUTHOR ADDRESS: (a)Div. Haematol., Hanson Centre Cancer Res., Inst. Med. Vet. Sci., PO Box 14 Rundle Mall, Adelaide**Australia

JOURNAL: Biochemical Journal 338 (1):p61-70 Feb. 15, 1999

ISSN: 0264-6021

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: CD151 (PETA-3/SFA-1) is a member of the transmembrane 4 superfamily (TM4SF) of cell-surface proteins and is expressed abundantly both on the cell surface and in intracellular membranes by the haemopoietic cell lines M07e, HEL and K562. In the presence of mild detergent (CHAPS), CD151 co-immunoprecipitated with integrin alpha4beta1, alpha5beta1, alpha6beta1 and alphaIIIBbeta3. The association of CD151 with alpha4beta1 and alpha5beta1 seemed to be constitutive, as it was not modified by treatment of M07e cells with cytokines that regulate integrin function by 'inside-out' signalling. CD151 also associated with other tetraspans in an apparently cell-type-specific fashion, as defined by its co-precipitation with CD9, CD63 and **CD81** from M07e cells, but not from K562 cells, which express similar levels of these proteins. F(ab')2 fragments of monoclonal antibodies (mAbs) against CD151 caused homotypic adhesion of HEL and K562 cells that was dependent on energy and cytoskeletal integrity and was augmented in the presence of RGDS peptides. The adhesion was not blocked by function-**inhibiting** mAbs against betal or beta3 integrins, suggesting that cell-cell adhesion was not mediated by the binding of integrin to a cell-associated ligand. Furthermore, mAb CD151 did not affect adhesion of the cells to fibronectin, laminin, collagen or fibrinogen, which are ligands for alpha4beta1, alpha5beta1, alpha6beta1 and alphaIIIBbeta3 integrins. Taken together, these results indicate that the ligation of CD151 does not induce the up-regulation of integrin avidity, but might act as a component of integrin signalling complexes.

1999

5/3,AB/81 (Item 10 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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11606591 BIOSIS NO.: 199800388329

Inhibition of replication of drug-resistant HIV type 1 isolates by polypurine tract-specific oligodeoxynucleotide TFO A.

AUTHOR: Jendis Jorg; Strack Bettina; Moelling Karin(a)

AUTHOR ADDRESS: (a)Inst. Med. Virol., Univ. Zurich, Gloriastrasse 30, CH-8028 Zurich**Switzerland

JOURNAL: AIDS Research and Human Retroviruses 14 (11):p999-1005 July 20, 1998

ISSN: 0889-2229

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: A 54-base-long oligodeoxynucleotide (ODN) termed triple helix-forming oligonucleotide A (TFO A), designed against the 3'-polypurine tract (PPT) of the human immunodeficiency virus type 1

(HIV-1), exhibits long-term efficacy in antiretroviral treatment. Viral replication of strains propagated in this laboratory as well as primary patient isolates are **inhibited** by TFO A, whereas ODNs with a randomized sequence but identical base composition show no effect. TFO A **inhibits** proviral DNA synthesis. To learn more about the molecular mechanism of function of TFO A, three HIV-1 isolates whose reverse transcriptase (RT) exhibits resistance against RT **inhibitors** were analyzed. They exhibit resistance against azidothymidine, dideoxyinosine, deoxythiacytidine, and the nonnucleoside **inhibitor** nevirapine. HIV-1 replication in TFO A-treated T cell cultures was assessed by monitoring p24 viral core antigen production and syncytium formation. No p24 antigen or syncytia were detected for up to 30 days when cells that had been infected with wild-type virus received TFO A. Similarly, replication of all three mutant HIV-1 strains was completely **inhibited** by TFO A treatment during the whole duration of the culturing period. No viral breakthrough was detectable. These results indicate that TFO A interferes with functions of the replicative cycle distinct from polymerization by the RT.

1998

5/3,AB/82 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08311570 BIOSIS NO.: 000094073893
A MEMBER OF THE TETRA SPANS TRANSMEMBRANE PROTEIN SUPERFAMILY IS RECOGNIZED BY A MONOCLONAL ANTIBODY RAISED AGAINST AN HLA CLASS I-DEFICIENT LYMPHOKINE-ACTIVATED KILLER-SUSCEPTIBLE B LYMPHOCYTE LINE CLONING AND PRELIMINARY FUNCTIONAL STUDIES
AUTHOR: GIL M L; VITA N; LEBEL-BINAY S; MILOUX B; CHALON P; KAGHAD M; MARCHIOL-FOURNIGAULT C; CONJEAUD H; CAPUT D; ET AL
AUTHOR ADDRESS: I.G.R., P.R.I. LAB. D'IMMUNOLOGIE CELLULAIRE, UA 1156 CNRS, 39, RUE CAMILLE DESMOULINS, 94800 VILLEJUIF, FR.
JOURNAL: J IMMUNOL 148 (9). 1992. 2826-2833. 1992
FULL JOURNAL NAME: Journal of Immunology
CODEN: JOIMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The IA4 mAb was identified among a series of antibodies raised in BALB/c mice after immunization against a HLA class I-deficient, lymphokine-activated killer (LAK)-susceptible EBV-B lymphocyte line. The IA4 antibody was selected because of its high expression, in the range of 105 to 25 .times. 105 sites/cell, on several B lymphocyte lines (EBV-transformed or Burkitt) and monocytic lines such as HL60 and U937, and because its expression was correlated with both target susceptibility to LAK lysis and reduced expression of HLA class I surface Ag on two pairs of EBV-B-transformed cell lines (721/721.134 and MM/10F2). Despite the strategy followed to raise the mAb and the correlation mentioned above, no direct role of the IA4 molecules in LAK susceptibility has been established, since the IA4 molecule is poorly expressed on the sensitive targets Daudi and K562; moreover, the IA4 antibody did not affect reproducibly the in vitro killing of positive target cells by LAK effectors. The IA4 antibody was poorly immunoprecipitating and the surface molecule recognized was identified by gene cloning following an expression strategy using a U937 cDNA library transfected in COS cells, and a screening strategy based on membrane expression of IA4 molecule. The IA4 cDNA is virtually identical to "R2", a mRNA species previously identified in activated human T cells by subtractive hybridization. The IA4 cDNA contains an open reading frame coding for a protein 267 amino acids long with four potential transmembrane domains and one large external hydrophilic domain of about 110 amino acids, possibly

glycosylated. The encoded protein belongs to a family of surface molecules, the tetra spans transmembrane proteins superfamily, all displaying the four transmembrane domains, expressed on various cell types including lymphocytes (CD9, CD37, CD53, **TAPA-1**), melanoma cells (ME491), and intestinal cells (CO-029). These molecules have been reported to be involved in cell activation and cell death. Surprisingly, the *Schistosoma mansoni* Ag Sm23 displays significant homologies with this family. The IA4 molecule is a widely distributed surface marker expressed on circulating lymphocytes and monocytes, newborn thymocytes and the cell lines mentioned above. The IA4 molecule expression is up-regulated upon cell activation. Weakly expressed on resting peripheral T and B lymphocytes and large granular lymphocytes (NK), its expression roughly doubles after activation by PHA, (*Staphylococcus aureus* Cowan I, and IL-2, respectively. The IA4 molecule expression can be upregulated also by cytokines, as observed on U937 and Daudi cells after in vitro treatment by TNF and IL-4, but not by IL-1 or IL-6. The IA4 membrane protein has signaling functions as it induces, within second, calcium mobilization from the intracellular calcium pool in U937 cells. The IA4 antibody **inhibits**, in a dose-dependent manner, the activation of peripheral B lymphocytes stimulated by the mitogen SAC, *Staphylococcus aureus* Cowan I.

1992